The following tables display Dr. Derr's analyses in a similar format to that presented for the Novo analyses in Tables 7.1.3.3.1.3.2, 7.1.3.3.1.3.4 and 7.1.3.3.1.3.6 above.

Table 7.1.3.3.1.3.13: Incidence Ratio, FDA Stratified Exact Analyses, All (Serious + Nonserious) Treatment-Emergent MACE, Broad SMQ and FDA Custom Endpoints

Comparator			MACE Endpoint		Pop		Point Estimate (95% CI)
Total Comp	PBO	AC	FDA Custom	Broad SMQ	A	B	
x			x		x		0.72 (0.30, 1.74)
x				x	x		0.86 (0.55, 1.41)
x			x			x	0.80 (0.39, 1.64)
x				x		x	0.90 (0.60, 1.36)
	x		x		x		0.78 (0.19, 4.76)
	x			x	x		1.04 (0.48, 2.17)
	x		x			x	0.92 (0.28, 3.97)
	x			x		x	1.10 (0.56, 2.31)
		x	x		x		0.68 (0.26, 1.83)
		x		x	x		0.82 (0.48, 1.33)
		x	x			x	0.76 (0.35, 1.72)
		x		x		x	0.84 (0.53, 1.35)

Source: Dr. Derr's Tables 7.1.3.3.1.3.9, 7.1.3.3.1.3.10, 7.1.3.3.1.3.11 and 7.1.3.3.1.3.12 above

Table 7.1.3.3.1.3.14: Incidence Ratio, FDA Asymptotic Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All (Serious + Nonserious) Treatment-Emergent MACE, Broad SMQ and FDA Custom Endpoints

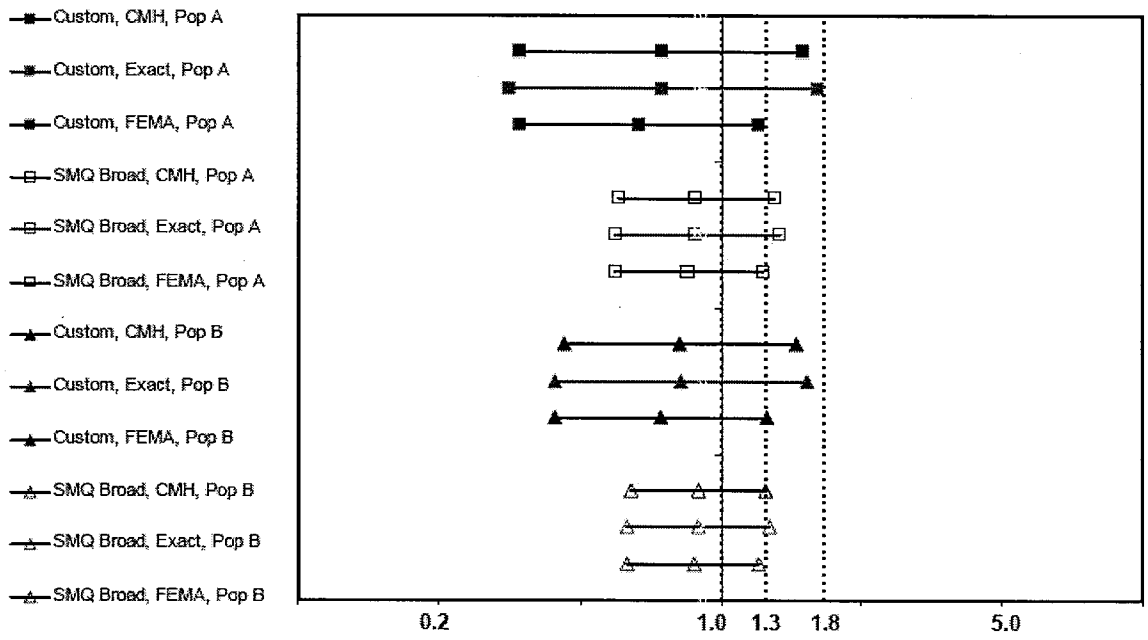
Comparator			MACE Endpoint		Pop		Point Estimate (95% CI)
Total Comp	PBO	AC	FDA Custom	Broad SMQ	A	B	
x			x		x		0.63 (0.32, 1.24)
x				x	x		0.83 (0.55, 1.27)
x			x			x	0.71 (0.39, 1.30)
x				x		x	0.86 (0.59, 1.24)
	x		x		x		0.52 (0.21, 1.25)
	x			x	x		0.86 (0.45, 1.65)
	x		x			x	0.60 (0.26, 1.39)
	x			x		x	0.89 (0.50, 1.60)
		x	x		x		0.60 (0.27, 1.31)
		x		x	x		0.79 (0.49, 1.28)
		x	x			x	0.68 (0.34, 1.37)
		x		x		x	0.83 (0.54, 1.27)

Source: Dr. Derr's Tables 7.1.3.3.1.3.9, 7.1.3.3.1.3.10, 7.1.3.3.1.3.11 and 7.1.3.3.1.3.12 above

The following three figures include vertical bars to mark the boundaries of 1.3 and 1.8, which are the previously discussed upper boundaries of interest for the 95% confidence interval specified in the Guidance for evaluation of cardiovascular risk of diabetes products. In each of the figures, both Novo (CMH) and FDA (Exact, FEMA) analyses are presented. Labels to the left specify the endpoint, population, and analysis method. For each horizontal bar, the middle symbol

represents the point estimate, and outer symbols represent the 95% confidence interval boundaries.

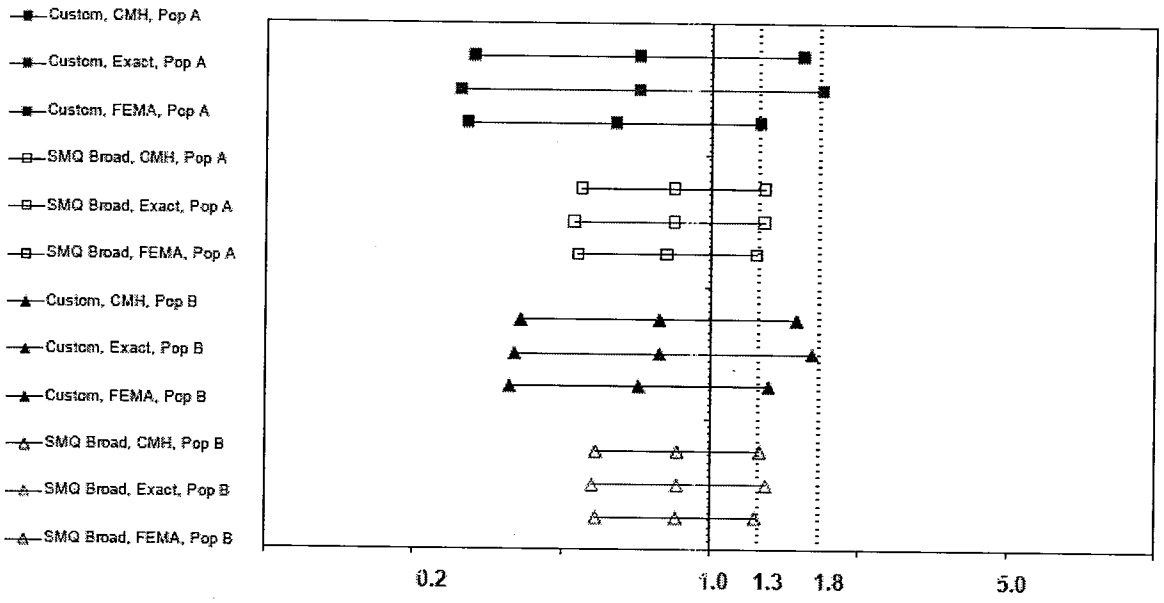
Figure 7.1.3.3.1.3.13: MACE Analyses by Three Estimation Methods, Liraglutide versus Total Comparator



Source: Dr. Derr's Advisory Committee presentation, 2 Apr 2009

For the analyses included in this figure, for comparisons of liraglutide to total comparator, all point estimates are <1, favoring liraglutide. When examining the upper bound of the 95% confidence interval, all values fall to the left of the 1.8 boundary line, but are near or to the right of the 1.3 boundary line. When examining the upper bounds as a group, they don't vary a great deal in value, supporting that these results were not very sensitive to analysis method.

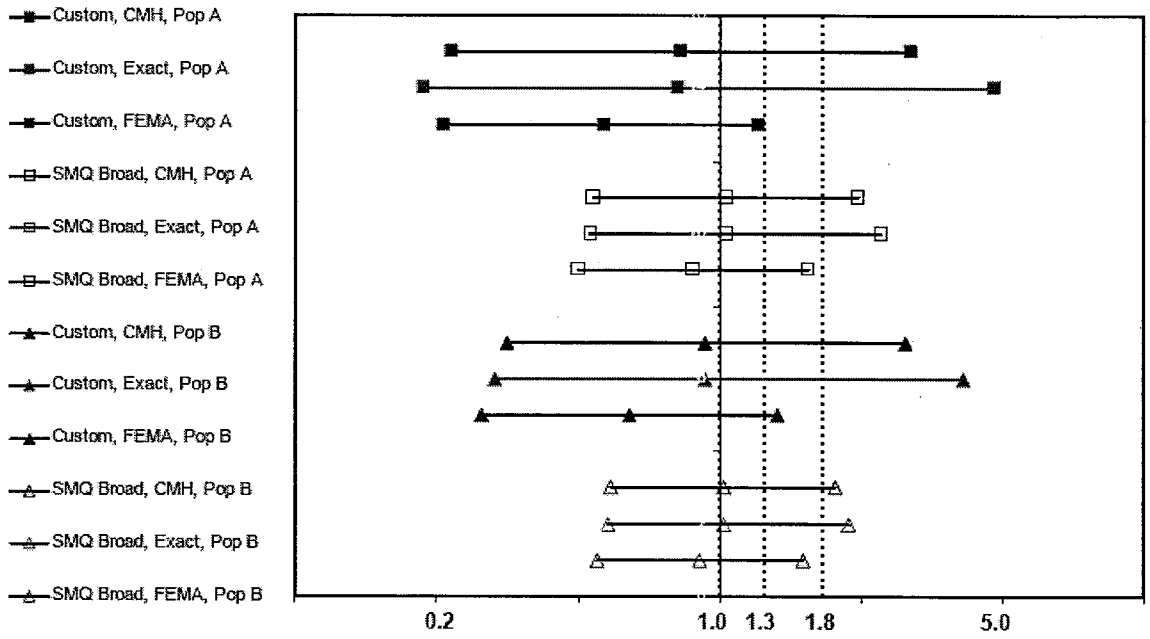
Figure 7.1.3.3.1.3.14: MACE Analyses by Three Estimation Methods, Liraglutide versus Active Control



Source: Dr. Derr's Advisory Committee presentation, 2 Apr 2009

For comparisons of liraglutide to active comparator, the results are qualitatively similar to those for comparisons to total comparator. Point estimates are <1. Upper bounds, with one exception, are <1.8, and most are at or above 1.3. There was a small degree of sensitivity to analysis method.

Figure 7.1.3.3.1.3.15: MACE Analyses by Three Estimation Methods, Liraglutide versus Placebo



Source: Dr. Derr's Advisory Committee presentation, 2 Apr 2009

In contrast to the preceding two figures, the figure for liraglutide versus placebo is somewhat different in terms of point estimates and upper bounds. Point estimates are not always <1, and sometimes are not favoring liraglutide. The upper bound is usually >1.8. There is more variability in the upper bound, reflecting the previously mentioned sensitivity to method.

The following listing shows all MACE events which occurred for the above 3 endpoints, and indicates which events were included in each endpoint. If a patient had more than one event, those events are listed here, but only the first event was included in the analyses.

Table 7.1.3.3.1.3.15: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
4505	2072	LGT 0.6 mg	Cerebrovascular disorder	26	y	y		y	y
9410	1310	"	Cerebral hemorrhage	84	y	y		y	y
49002	1701	"	Cerebral arteriosclerosis	358				y	y
51002	1701	"	Blood CPK increased	249				y	

Table 7.1.3.3.1.3.15: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
124003	1572	"	"	184	y			y	
213002	"	"	"	1	y			y	
227006	"	"	MI	416		y	y	y	y
270001	"	"	Acute MI	244		y	y	y	y
300015	"	"	"	299		y	y	y	y
358003	"	"	Coronary artery occlusion	187		y		y	y
372006	"	"	Acute coronary syndrome	16	y	y		y	y
394003	"	"	Hemorrhage intracranial	388		y		y	y
403005	"	"	Blood CPK incr	544				y	
587037	1436	"	"	182	y			y	
617010	"	"	"	1	y			y	
619002	"	"	"	1	y			y	
9024	1700	LGT 0.9 mg	MI	14	y	y	y	y	y
29001	"	"	Blood CPK incr	28	y	y		y	
"	"	"	"	330				y	
29003	1701	"	Cerebral infarction	178[1]			y	y	y
51003	1700	"	Acute MI	160	y	y	y	y	y
51004	"	"	Cerebral infarction	233			y	y	y
52002	"	"	MI	191		y	y	y	y
67002	"	"	TIA	191				y	y
131058	1807	LGT 1.2 mg	Blood CPK incr	99	y			y	
158005	1573	"	Carotid artery stenosis	40	y			y	y
194012	"	"	"	78	y			y	y
205016	"	"	Blood CPK incr	248	y			y	
213018	1572	"	"	84	y			y	
216005	1573	"	"	205	y			y	
239001	1572	"	"	558				y	
239004	"	"	"	280				y	
239005	"	"	"	184	y			y	
253002	"	"	Paresis	21	y			y	
288002	"	"	CVA	149	y	y	y	y	y
326009	"	"	Subarachnoid hemorrhage	292		y		y	y
332007	"	"	Acute MI	133	y	y	y	y	y
332025	1574	"	MI	183	y		y	y	y
375003	1572	"	"	337		y	y	y	y

Table 7.1.3.3.1.3.15: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
403012	"	"	Blood CPK incr	1	y			y	
516011	1573	"	MI	167	y	y	y	y	y
547011	1436	"	TIA	88	y			y	y
562010	"	"	Blood CPK incr	85	y			y	
568002	"	"	Acute MI	89	y	y	y	y	y
120004	1573	LGT 1.8 mg	MI	367		y	y	y	y
121022	1807	"	CVA	13	y	y	y	y	y
136005	1573	"	Blood CPK incr	199	y			y	
172065	1807	"	"	113	y			y	
188010	1573	"	"	359	y			y	
217003	1572	"	"	84	y			y	
253010	1573	"	"	359	y			y	
273015	1572	"	"	272				y	
324019	1574	"	Coronary artery occlusion	26	y			y	y
326011	1797	"	Blood CPK incr	184	y			y	
343002	1572	"	"	184	y			y	
381003	1574	"	"	1	y			y	
401002	1797	"	Cerebellar infarction	103	y	y	y	y	y
496011	1436	"	ECG Q wave abnl	188	y			y	
514001	1797	"	Blood CPK incr	84	y			y	
546028	1436	"	"	86	y			y	
596001	"	"	Acute MI	182	y		y	y	y
622001	"	"	MI	181	y	y	y	y	y
659002	1697	"	Blood CPK incr	91	y			y	
714012	"	"	CVA	62	y	y	y	y	y
751001	"	"	Blood CPK incr	1	y			y	
826029	"	"	TIA	89	y			y	y
829002	"	"	Acute MI	154	y	y	y	y	y
121001	1807	LGT 2.4 mg	Blood CPK incr	142	y			y	
171039	"	LGT 3.0 mg	"	111	y			y	
172063	"	"	TIA	29	y	y		y	y
29004	1700	AC	Thalamus hemorrhage	199[1]				y	y
"	"	"	Cerebral infarction	305		y	y	y	y
62002	"	"	MI	233[1]		y	y	y	y
63006	"	"	Cerebral infarction	231		y	y	y	y

Table 7.1.3.3.1.3.15: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
103006	1807	"	Blood CPK incr	229				y	
133036	"	"	"	87	y			y	
164001	1572	"	MI	176	y	y	y	y	y
171023	1807	"	Blood CPK incr	30	y			y	
171056	"	"	"	57	y			y	
178012	1572	"	Carotid arteriosclerosis	272				y	y
183012	1573	"	Blood CPK incr	84	y			y	
"	"	"	"	286	y			y	
201004	1572	"	MI	45	y	y	y	y	y
203004	"	"	Paralysis	16	y			y	
273002	1573	"	Acute MI	24	y	y	y	y	y
275001	"	"	MI	218	y	y	y	y	y
300004	1572	"	Blood CPK incr	1	y			y	
"	"	"	TIA	126	y			y	y
"	"	"	Carotid artery stenosis	135	y	y		y	y
300008	"	"	"	188				y	y
327016	1797	"	CVA	145	y	y	y	y	y
372010	1572	"	Blood CPK incr	182	y			y	
372011	"	"	"	182	y			y	
381007	"	"	"	1	y			y	
489004	1797	"	Acute MI	61	y	y	y	y	y
528012	1436	"	Blood CPK incr	87	y			y	
528019	"	"	"	82	y			y	
546009	"	"	"	92	y			y	
547008	"	"	"	84	y			y	
587017	"	"	"	1	y			y	
702006	1697	"	MI	153	y	y	y	y	y
713009	"	"	Acute MI	142	y	y	y	y	y
749007	"	"	TIA	153	y	y		y	y
"	"	"	Carotid artery stenosis	157	y			y	y
770002	"	"	Ischemic stroke	10	y	y	y	y	y
827005	"	"	Acute MI	117	y	y	y	y	y
827020	"	"	Carotid artery stenosis	141	y	y		y	y
4812	2072	PBO	Cerebrovascular disorder	60	y	y		y	y
7009	1701	"	Carotid artery stenosis	308				y	y
9006	"	"	Blood CPK incr	252				y	
12002	"	"	"	308				y	
41002	"	"	Brain stem infarction	354			y	y	y
237005	1572	"	Blood CPK incr	1	y			y	

Table 7.1.3.3.1.3.15: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
314006	1574	"	"	126	y			y	
381007	"	"	"	1	y			y	
388010	"	"	"	135	y			y	
431003	1436	"	MI	182	y	y	y	y	y
596002	"	"	MI	183	y		y	y	y
619010	"	"	Blood CPK incr	185	y			y	
689012	1697	"	Acute MI	78	y	y	y	y	y

Source: NDA 22341, subm stamp date 21 Jan 2009, Appendix A, Applicant's Listings 1 and 2, pages 1-11
1 Patient had only month and year data for onset of event; date imputed to first day of month (Source: NDA 22341 subm stamp date 13 Feb 2009, pg 7)
Abbreviations: abnl = abnormal, CPK = creatine phosphokinase, CVA = cerebrovascular accident, ECG = electrocardiogram, ID = identification, LGT = liraglutide, MedDRA = Medical Dictionary for Regulatory Activities, MI = myocardial infarction, Pop = time period population, Pt = patient, SAE = serious adverse event, SMQ = Standard MedDRA Query, TIA = transient ischemic attack, Tx = treatment

Observations related to the above table include:

- The most common events in the FDA Custom endpoint which occurred were myocardial infarction (15 events), acute myocardial infarction (11 events), cerebral infarction (4 events) and cerebrovascular accident (4 events).
- A large percentage of the events which occurred in the "Broad SMQ" endpoint, but not in the "FDA Custom" or "Narrow SMQ" endpoints were events of "blood creatine phosphokinase increased". A total of 55/120 (46%) of the total "Broad SMQ" events were these events of increased CPK. This event term accounted for 55/58 (95%) of events which occurred in the Broad SMQ but did not occur in the Narrow SMQ. Therefore, almost all of the increased specificity of the Narrow SMQ endpoint (compared to the Broad SMQ endpoint) was accounted for by this one term. The term accounted for 55/82 (67%) of events which occurred in the Broad SMQ but did not occur in the FDA Custom MACE. A total of 11/55 (20%) of the total events of increased CPK were reported to have occurred on Day 1 of study, which would suggest that, in these patients, elevation of CPK might have been present at baseline, and might not actually be a treatment effect.
- Other events which occurred in the Broad SMQ endpoint, but were not included in the FDA Custom endpoint, included carotid artery stenosis (2 LGT NSAE, 2 AC SAE, 2 AC NSAE, 1 PBO NSAE), transient ischemic attack (1 LGT SAE, 3 LGT NSAE, 1 AC SAE, 1 AC NSAE), coronary artery occlusion (1 LGT SAE, 1 LGT NSAE), cerebrovascular disorder (1 LGT SAE, 1 PBO SAE), acute coronary syndrome (1 LGT SAE), cerebral hemorrhage (1 LGT SAE), hemorrhage intracranial (1 LGT SAE), subarachnoid hemorrhage (1 LGT SAE), carotid arteriosclerosis (1 AC NSAE), cerebral arteriosclerosis (1 LGT NSAE), electrocardiogram Q wave abnormal (1 LGT NSAE), paresis (1 LGT NSAE), paralysis (1 AC NSAE) and thalamus hemorrhage (1 AC NSAE).

The following table displays the most commonly occurring event terms for events which actually occurred.

Table 7.1.3.3.1.3.16: Most Commonly Occurring Event Terms for Events Which Actually Occurred, MACE Analyses

Term	Total N=6638 n (%)	LGT N=4257 n (%)	Comp N=2381 n (%)	In Broad SMQ?	In FDA Custom?
Blood CPK increased	52 (0.8)	32 (0.8)	20 (0.8)	y	
MI	15 (0.2)	8 (0.2)	7 (0.3)	y	y
Acute MI	12 (0.2)	7 (0.2)	5 (0.2)	y	y
Carotid artery stenosis	7 (0.1)	2 (<0.1)	5 (0.2)	y	
TIA	6 (0.1)	4 (0.1)	2 (0.1)	y	
Cerebral infarction	4 (0.1)	2 (<0.1)	2 (0.1)	y	y
CVA	4 (0.1)	3 (0.1)	1 (<0.1)	y	y

Source: Table 7.1.3.3.1.3.15 above

As discussed earlier, the most commonly occurring event term was "blood CPK increased". The vast majority of these events were nonserious. Only one patient (300004, Study 1572, AC-treated) who had an event of CPK elevation also had another MACE that was not CPK elevation. For this patient, the event of blood CPK elevation occurred on Day 1, an event of TIA occurred on Day 126, and an event of carotid artery stenosis occurred on Day 135. Because the CPK elevation was present at baseline, it was unlikely to be caused by treatment, and because it occurred so distantly from the subsequent events, it was unlikely to be related to them. Overall, in the liraglutide development program, the occurrence of an event of CPK elevation did not appear to portend subsequent serious cardiovascular events. Also of note from the table above is that events of MI were infrequent, and occurred at similar rates between liraglutide and comparator groups.

There did not appear to be a relationship between LGT dose and the incidence of events within any of the three composite endpoints, as shown in the tables below. For each of the composite endpoints, among liraglutide-treated patients, the highest numerical incidence of events tended to occur in the 1.2 mg/day dose group.

Table 7.1.3.3.1.3.17: Incidence of MACE Events by Liraglutide Dose, Time Period Population A, All Treatment-Emergent Events

Dose Group	N	FDA Custom		Broad SMQ		Narrow SMQ	
		n	%	n	%	n	%
LGT <0.6 mg	275	0	0	0	0	0	0
LGT 0.6 mg	693	0	0	7	1.0	2	0.3
LGT >0.6 and <1.2 mg	512	2	0.4	4	0.8	3	0.6
LGT 1.2 mg	991	5	0.5	16	1.6	8	0.8
LGT >1.2 and <1.8 mg	44	0	0	0	0	0	0
LGT 1.8 mg	1455	6	0.4	21	1.4	8	0.6

Table 7.1.3.3.1.3.17: Incidence of MACE Events by Liraglutide Dose, Time Period Population A, All Treatment-Emergent Events

Dose Group	N	FDA Custom		Broad SMQ		Narrow SMQ	
		n	%	n	%	n	%
LGT >1.8 mg	287	0	0	3	1.1	1	0.4
Total LGT	4257	13	0.3	51	1.2	22	0.5
PBO	907	3	0.3	9	1.0	4	0.4
Active Comp	1474	10[1]	0.7	26	1.8	13	0.9
Total Comp	2381	13	0.5	35	1.5	17	0.7

Source: Applicant's Tables 1-3, beg pg 30, Appendix B, NDA 22341 submission received 21 Jan 2009
1 The 21 Jan 2009 submission included 9 events in this category, but one additional event reported in 13 Feb 2009 submission

Table 7.1.3.3.1.3.18: Incidence of MACE Events by Liraglutide Dose, Time Period Population A, Serious Treatment-Emergent Events

Dose Group	N	FDA Custom		Broad SMQ		Narrow SMQ	
		n	%	n	%	n	%
LGT <0.6 mg	275	0	0	0	0	0	0
LGT 0.6 mg	693	0	0	2	0.3	2	0.3
LGT >0.6 and <1.2 mg	512	2	0.4	4	0.8	3	0.6
LGT 1.2 mg	991	4	0.4	4	0.4	4	0.4
LGT >1.2 and <1.8 mg	44	0	0	0	0	0	0
LGT 1.8 mg	1455	5	0.3	5	0.3	5	0.3
LGT >1.8 mg	287	0	0	1	0.4	1	0.4
Total LGT	4257	11	0.3	16	0.4	15	0.4
PBO	907	2	0.2	3	0.3	3	0.3
Active Comp	1474	10[1]	0.7	13	0.9	13	0.9
Total Comp	2381	12	0.5	16	0.7	16	0.7

Source: Applicant's Tables 4-6, beg pg 36, Appendix B, NDA 22341 submission received 21 Jan 2009
1 The 21 Jan 2009 submission included 9 events in this category, but one additional event reported in 13 Feb 2009 submission

Results by liraglutide dose were qualitatively similar for the patients included in time period Population B (Source: NDA 22341, submission stamp date 21 Jan 2009, Tables 7-12, beginning serial page 42).

7.1.3.3.1.4: Other MACE Analyses

Prior to the "uniform" MACE information request described above, Novo had submitted other MACE analyses, using a different endpoint. Please see the column entitled "Prior Novo MACE" in Table 7.1.3.3.1.2 above for the terms included in this endpoint. This endpoint was defined *post hoc*, and included only terms for events that actually occurred, rather than prespecified terms from a Standard MedDRA Query. That is, the Broad Standard MedDRA Query endpoint

included a predefined standard set of *terms*; from this broad set of event terms, there were some actual events which occurred, but for many terms, no event actually occurred. The "Prior Novo MACE" endpoint was picked by looking only at *events* which had actually occurred, and choosing those events which appeared to be relevant, rather than choosing a list of terms, and then seeing if any events from that list had occurred. As mentioned earlier, two terms which occurred in this endpoint, but which do not appear in the MedDRA Standard Queries, are cardiac arrest and circulatory collapse. The analyses included all completed Phase 2 and Phase 3 trials in diabetes and obesity, with or without the extension periods for these trials.

Table 7.1.3.3.1.4.1: Incidence Ratio, Liraglutide versus Comparator, Analyses of "Prior Novo MACE" Endpoint

Comparator			Type of Events		Pop		Point Estimate (95% CI)
Total Comp	PBO	Active Comp	All TEAE	Serious Only	Main Period	Main + Ext	
x			x		x		0.63 (0.29, 1.35)
x				x	x		0.65 (0.25, 1.65)
x			x			x	0.80 (0.45, 1.42)
x				x		x	0.91 (0.46, 1.78)
	x		x		x		0.67 (0.21, 2.12)
	x			x	x		0.80 (0.16, 3.94)
	x		x			x	0.89 (0.33, 2.39)
	x			x		x	1.43 (0.32, 6.33)
		x	x		x		0.61 (0.26, 1.42)
		x		x	x		0.62 (0.23, 1.64)
		x	x			x	0.77 (0.41, 1.45)
		x		x		x	0.83 (0.41, 1.68)

Source: NDA 22341, submission stamp date 7 Oct 2008, Applicant's Tables 2-3, 2-4 (pg 10), 2-5 (pg 11), and 2-6 (pg 12)
Cox proportional hazard regression model, stratified by trial

Qualitatively, the results of these analyses were similar to those for the FDA Custom, Broad SMQ and Narrow SMQ analyses. That is, for total and active comparator, the point estimate tended to be less than one, and the upper bound of the 95% confidence interval did not tend to exceed 1.8. For comparison to placebo, the upper bound did exceed 1.8, but as shown in Table 7.1.3.3.1.4.2 below, the number of events in placebo groups was very small.

As with the Custom FDA, Broad SMQ and Narrow SMQ endpoints, the overall number of events was small, as shown in the following table.

Table 7.1.3.3.1.4.2: Numbers of MACE Events for "Prior Novo MACE" Endpoint

Type of Event	Total LGT N=4257 PY=2882	PBO N=907 PY=449	AC N=1474 PY=1038	Total Comp N=2381 PY=1486
CV deaths	0	1 (0.1)	1 (0.1)	2 (0.1)
Serious MACE	22 (0.5)	2 (0.2)	13 (0.9)	15 (0.6)
Nonserious MACE	8 (0.2)	4 (0.4)	3 (0.2)	7 (0.3)
Total MACE	29 (0.7)	5 (0.6)	16 (1.1)	21 (0.9)

Source: NDA 22341, submission stamp date 7 Oct 2008, Applicant's Table 1, Appendix A, pg 15

7.1.3.3.1.5. Overall Cardiovascular Event Summaries

The above analyses have focused on events of myocardial infarction, stroke and cardiovascular death. Other types of cardiovascular events occurred, and the following tables summarize the incidence of all potential cardiovascular events. Not all listed events are known to be cardiovascular in etiology. For example, the event terms "chest pain" and "edema" may have non-cardiovascular etiologies. However, these tables are provided to give the broadest possible overview of the incidence of potential cardiovascular events.

7.1.3.3.1.5.1. Serious Adverse Potentially Cardiovascular Events

The following table includes all serious adverse events that potentially involved the cardiac and vascular systems. This grouping will include more terms than those specified for the MACE analyses. Please note that this table includes events which had occurred at the time of the initial NDA submission. The MACE analyses above include additional data from the safety update which was submitted four months later, and therefore the number of events may differ slightly for certain MACE terms.

Table 7.1.3.3.1.5.1: Serious Potential Cardiovascular Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
Cardiac	Any	37	0.9	17.4	18	0.8	16.7
	Angina pectoris	7	0.2	3.1	3	0.1	2.6
	Acute myocardial infarction	5	0.1	2.2	4	0.2	3.5
	Myocardial infarction	5	0.1	2.2	5	0.2	4.4
	Coronary artery disease	4	0.1	1.8	1	<0.1	0.9
	Atrial fibrillation	2	<0.1	0.9	1	<0.1	0.9
	Cardiac failure congestive	2	<0.1	0.9	0	0	0
	Myocardial ischemia	2	<0.1	0.9	0	0	0
	Supraventricular tachycardia	2	<0.1	0.9	0	0	0
	Acute coronary syndrome	1	<0.1	0.4	0	0	0

Table 7.1.3.3.1.5.1: Serious Potential Cardiovascular Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
	Angina unstable	1	<0.1	0.4	0	0	0
	Atrial flutter	1	<0.1	0.4	1	<0.1	0.9
	Cardiac arrest	1	<0.1	0.4	0	0	0
	Cardiac failure	1	<0.1	0.4	0	0	0
	Congestive cardiomyopathy	1	<0.1	0.4	0	0	0
	Coronary artery occlusion	1	<0.1	0.4	0	0	0
	Right ventricular failure	1	<0.1	0.4	0	0	0
	Tachycardia	1	<0.1	0.4	1	<0.1	0.9
	Tachycardia paroxysmal	1	<0.1	0.4	0	0	0
	Coronary artery stenosis	0	0	0	1	<0.1	0.9
	Ischemic cardiomyopathy	0	0	0	1	<0.1	0.9
	Ventricular tachycardia	0	0	0	1	<0.1	0.9
Vascular disorders	Any	3	0.1	1.3	4	0.2	3.5
	Arteriosclerosis	1	<0.1	0.4	0	0	0
	Orthostatic hypotension	1	<0.1	0.4	0	0	0
	Peripheral vascular disorder	1	<0.1	0.4	0	0	0
	Aortic aneurysm	0	0	0	1	<0.1	0.9
	Arterial stenosis limb	0	0	0	1	<0.1	0.9
	Arteriosclerosis obliterans	0	0	0	1	<0.1	0.9
	Hypertension	0	0	0	1	<0.1	0.9
Nervous system disorders	Any (includes noncardiovascular events)	18	0.4	8.0	7	0.3	6.1
	Cerebrovascular accident	3	0.1	1.3	0	0	0
	Syncope	2	<0.1	0.9	0	0	0
	Cerebral hemorrhage	1	<0.1	0.4	0	0	0
	Cerebrovascular disorder	1	<0.1	0.4	1	<0.1	0.9
	Hemorrhage intracranial	1	<0.1	0.4	0	0	0
	Loss of consciousness	1	<0.1	0.4	0	0	0
	Subarachnoid hemorrhage	1	<0.1	0.4	0	0	0
	Transient ischemia attack	1	<0.1	0.4	1	<0.1	0.9
	Carotid artery stenosis	0	0	0	2	0.1	1.8
	Ischemic stroke	0	0	0	1	<0.1	0.9
General disorders and administration site conditions	Any (includes noncardiovascular events)	8	0.2	3.6	6	0.3	5.3
	Chest pain	5	0.1	2.2	4	0.2	3.5
	Noncardiac chest pain	1	<0.1	0.4	1	<0.1	0.9
Respiratory, thoracic and mediastinal disorders	Any (includes noncardiovascular events)	5	0.1	2.2	4	0.2	3.5
	Pulmonary embolism	2	<0.1	0.9	1	<0.1	0.9
	Pulmonary edema	0	0	0	1	<0.1	0.9

Table 7.1.3.3.1.5.1: Serious Potential Cardiovascular Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
Investigations	**Any (includes noncardiovascular events)**	2	<0.1	0.9	1	<0.1	0.9
	Heart rate increased	1	<0.1	0.4	0	0	0
	Electrocardiogram abnormal	0	0	0	1	<0.1	0.9

Source: Applicant's Table 72, beg pg 1123 ISS
Abbreviations: LGT = liraglutide; PY = patient-years

When considering all potential serious cardiovascular event terms, there did not appear to be an imbalance in any one term or group of terms for liraglutide versus non-liraglutide groups. However, it should be noted that the pooled safety database is somewhat different from the database used to compare the incidence of MACE events in liraglutide versus active comparator and liraglutide versus placebo comparator groups. This is because the MACE analyses that Dr. Derr and Novo conducted were stratified by study, and involved only those studies with the pertinent comparator.

In Section 7.1.2, when considering only serious adverse events in studies available at the time of NDA submission, there had been an imbalance in events of stroke or intracranial hemorrhage, not favoring liraglutide (7 LGT versus 1 non-LGT). However, when considering all MACE events presented in the expanded database in Table 7.1.3.3.1.5.1 above, there did not appear to be an imbalance for the composite of stroke or intracranial hemorrhage (9 LGT, 5 AC, 1 PBO; ratio 0.8:1 LGT versus non-LGT after accounting for approximately 2:1 randomization).

7.1.3.3.1.5.2. Combined Serious and Nonserious Adverse Cardiovascular Events

The following table includes all adverse events (serious and nonserious combined) that potentially involved the cardiac and vascular systems. This grouping will include more terms than those specified for the MACE analyses. Please note that this table includes events which had occurred at the time of the initial NDA submission. The MACE analyses above include additional data from the safety update which was submitted four months later, and therefore the number of events may differ slightly for certain MACE terms. Liraglutide incidence is broken down by dose.

Table 7.1.3.3.1.5.2.1: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
Cardiac	**Any**	25 (2.2)	32 (2.7)	57 (2.5)	6 (1.5)	31 (4.8)	3 (0.7)	46 (4.6)	2 (3.1)	45 (3.2)	6 (2.1)	139 (3.3)
	Palpitations	4 (0.4)	5 (0.4)	9 (0.4)	2 (0.5)	2 (0.3)		6 (0.6)		12 (0.9)	5 (1.7)	27 (0.6)
	Angina pectoris	3 (0.3)	3 (0.3)	6 (0.3)		9 (1.4)	1 (0.2)	5 (0.5)	1 (1.6)	4 (0.3)		20 (0.5)
	Tachycardia	2 (0.2)	3 (0.3)	5 (0.2)	2 (0.5)	2 (0.3)		5 (0.5)		4 (0.3)		13 (0.3)
	Myocardial infarction	2 (0.2)	4 (0.3)	6 (0.3)		1 (0.2)		3 (0.3)		2 (0.1)		6 (0.1)
	Ventricular extrasystoles	1 (0.1)	2 (0.2)	3 (0.1)		1 (0.2)		3 (0.3)		4 (0.3)		8 (0.2)
	Myocardial ischemia	1 (0.1)		1 (<0.1)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.3)	1 (1.6)	2 (0.1)		9 (0.2)
	AV block first degree	3 (0.3)	1 (0.1)	4 (0.2)		2 (0.3)	1(0.2)	2 (0.2)		1 (0.1)		6 (0.1)
	Acute myocardial infarction	1 (0.1)	3 (0.3)	4 (0.2)		2 (0.3)		2 (0.2)		2 (0.1)		6 (0.1)
	Atrial fibrillation		3 (0.3)	3 (0.1)		1 (0.2)				3 (0.2)	1 (0.3)	5 (0.1)
	Coronary artery disease		1 (0.1)	1 (<0.1)		1 (0.2)		2 (0.2)		3 (0.2)		6 (0.1)
	Bundle branch block left	2 (0.2)	2 (0.2)	4 (0.2)		1 (0.2)		1 (0.1)		1 (0.1)		3 (0.1)
	Bundle branch block right							1 (0.1)		4 (0.3)		5 (0.1)
	Supraventricular extrasystoles	1 (0.1)	1 (0.1)	2 (0.1)				2 (0.2)				2 (<0.1)
	Sinus tachycardia					2 (0.3)		2 (0.2)				4 (0.1)
	Left ventricular hypertrophy		2 (0.2)	2 (0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	Supraventricular tachycardia							1 (0.1)		2 (0.1)		3 (0.1)
	Sinus bradycardia	2 (0.2)		2 (0.1)						1 (0.1)		1 (<0.1)
	Cardiac failure							2 (0.2)		1 (0.1)		3 (0.1)
	Atrial flutter		1 (0.1)	1 (<0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	Ventricular tachycardia	1 (0.1)		1 (<0.1)						1 (0.1)		1 (<0.1)
	Tachycardia paroxysmal					1 (0.2)		1 (0.1)				2 (<0.1)
	Mitral valve incompetence	1 (0.1)	1 (0.1)	2 (0.1)								
	Left atrial dilatation		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)
	Extrasystoles		1 (0.1)	1 (<0.1)						1 (0.1)		1 (<0.1)
	Coronary artery stenosis	1 (0.1)	1 (0.1)	2 (0.1)								
	Coronary artery occlusion					1 (0.2)				1 (0.1)		2 (<0.1)

Table 7.1.3.3.1.5.2.1: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Congestive cardiomyopathy							1 (0.1)				1 (<0.1)
	Cardiac failure congestive							2 (0.2)				2 (<0.1)
	Cardiac arrest					1 (0.2)						1 (<0.1)
	Bundle branch block bilateral							1 (0.1)		1 (0.1)		2 (<0.1)
	Arrhythmia				2 (0.5)							2 (<0.1)
	Ventricular hypertrophy	1 (0.1)		1 (<0.1)								
	Tricuspid valve incompetence		1 (0.1)	1 (<0.1)								
	Sinus arrhythmia							1 (0.1)				1 (<0.1)
	Right ventricular failure									1 (0.1)		1 (<0.1)
	Pericardial effusion							1 (0.1)				1 (<0.1)
	Myocardial fibrosis							1 (0.1)				1 (<0.1)
	Mitral valve sclerosis									1 (0.1)		1 (<0.1)
	Ischemic cardiomyopathy		1 (0.1)	1 (<0.1)								
	Cardiac discomfort		1 (0.1)	1 (<0.1)								
	Bundle branch block					1 (0.2)						1 (<0.1)
	Bradycardia							1 (0.1)				1 (<0.1)
	AV block							1 (0.1)				1 (<0.1)
	Angina unstable							1 (0.1)				1 (<0.1)
	Acute coronary syndrome					1 (0.2)						1 (<0.1)
Vascular	Any	26 (2.3)	57 (4.9)	83 (3.7)	9 (2.2)	31 (4.8)	11 (2.6)	42 (4.2)	1 (1.6)	56 (4.0)	10 (3.5)	160 (3.8)
	Hypertension	15 (1.3)	40 (3.4)	55 (2.4)	5 (1.2)	15 (2.3)	1 (0.2)	21 (2.1)	1 (1.6)	30 (2.1)	1 (0.3)	74 (1.8)
	Vascular calcification	1 (0.1)	4 (0.3)	5 (0.2)		6 (0.9)		3 (0.3)		6 (0.4)	2 (0.7)	17 (0.4)
	Hematoma	3 (0.3)	2 (0.2)	5 (0.2)		4 (0.6)		1 (0.1)		4 (0.3)		9 (0.2)
	Hypotension		2 (0.2)	2 (0.1)			1 (0.2)	6 (0.6)		3 (0.2)	2 (0.7)	12 (0.3)
	Flushing	1 (0.1)		1 (<0.1)	2 (0.5)		1 (0.2)	2 (0.2)		2 (0.1)	2 (0.7)	9 (0.2)
	Hot flush		1 (0.1)	1 (<0.1)			3 (0.7)	1 (0.1)		3 (0.2)		7 (0.2)
	Aortic calcification		3 (0.3)	3 (0.1)		4 (0.6)				1 (0.1)	1 (0.3)	6 (0.1)

Table 7.1.3.3.1.5.2.1: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Arteriosclerosis				1 (0.2)	3 (0.5)		1 (0.1)		2 (0.1)		7 (0.2)
	Varicose vein		1 (0.1)	1 (<0.1)				2 (0.2)		2 (0.1)	1 (0.3)	5 (0.1)
	Orthostatic hypotension	1 (0.1)		1 (<0.1)		1 (0.2)		3 (0.3)		1 (0.1)		5 (0.1)
	Pallor				1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)				5 (0.1)
	Phlebitis		1 (0.1)	1 (<0.1)		1 (0.2)	1 (0.2)					2 (<0.1)
	Aortic arteriosclerosis		1 (0.1)	1 (<0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	Venous stasis	1 (0.1)		1 (<0.1)						1 (0.1)		1 <0.1)
	Thrombophlebitis						1 (0.2)				1 (0.3)	2 (<0.1)
	Lymphedema					1 (0.2)	1 (0.2)					2 (<0.1)
	Aortic aneurysm		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)
	Angiopathy					2 (0.3)						2 (<0.1)
	Venous thrombosis		1 (0.1)	1 (<0.1)								
	Vasodilation	1 (0.1)		1 (<0.1)								
	Thrombophlebitis superficial									1 (0.1)		1 (<0.1)
	Raynaud's phenomenon							1 (0.1)				1 (<0.1)
	Phlebitis superficial	1 (0.1)		1 (<0.1)								
	Peripheral vascular disorder									1 (0.1)		1 (<0.1)
	Peripheral arterial occlusive disease		1 (0.1)	1 (<0.1)								
	Ischemia		1 (0.1)	1 (<0.1)								
	Intermittent claudication		1 (0.1)	1 (<0.1)								
	Hypertensive crisis		1 (0.1)	1 (<0.1)								
	Essential hypertension										1 (0.3)	1 (<0.1)
	Deep vein thrombosis										1 (0.3)	1 (<0.1)
	Circulatory collapse	1 (0.1)		1 (<0.1)								
	Blood pressure fluctuation							1 (0.1)				1 (<0.1)
	Bleeding varicose vein									1 (0.1)		1 (<0.1)
	Arteriosclerosis obliterans		1 (0.1)	1 (<0.1)								

Table 7.1.3.3.1.5.2.1: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Arterial stenosis limb	1 (0.1)		1 (<0.1)								
	Aneurysm						1 (0.2)					1 (<0.1)
Nervous system	Any (includes non-CV events)	189 (16.8)	184 (15.8)	371 (16.3)	63 (15.7)	90 (14.0)	73 (17.5)	195 (19.6)	12 (18.8)	295 (21.0)	58 (20.1)	786 (18.7)
	Syncope	3 (0.3)	1 (0.1)	4 (0.2)	2 (0.5)	1 (0.2)		1 (0.1)		5 (0.4)	1 (0.3)	10 (0.2)
	Syncope vasovagal	1 (0.1)		1 (<0.1)			1 (0.2)	1 (0.1)		2 (0.1)	1 (0.3)	5 (0.1)
	Carotid artery stenosis	4 (0.3)	4 (0.2)					2 (0.2)				2 (<0.1)
	TIA		2 (0.2)	2 (0.1)				1 (0.1)		1 (0.1)	1 (0.3)	3 (0.1)
	CVA							1 (0.1)		2 (0.1)		3 (0.1)
	Global amnesia		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)
	Cerebrovasc disorder	1 (0.1)		1 (<0.1)			1 (0.2)					1 (<0.1)
	Aphonia	1 (0.1)		1 (<0.1)						1 (0.1)		1 (<0.1)
	Visual field defect		1 (0.1)	1 (<0.1)								
	Subarachnoid hemorrhage							1 (0.1)				1 (<0.1)
	Paresis							1 (0.1)				1 (<0.1)
	Paralysis		1 (0.1)	1 (<0.1)								
	Pallanesthesia					1 (0.2)						1 (<0.1)
	Ischemic stroke		1 (0.1)	1 (<0.1)								
	Hemorrhage intracranial					1 (0.2)						1 (<0.1)
	Cerebral hemorrhage					1 (0.2)						1 (<0.1)
	Carotid arteriosclerosis		1 (0.1)	1 (<0.1)								
	Ataxia							1 (0.1)				1 (<0.1)
	Amnesia		1 (0.1)	1 (<0.1)								
Musculoskeletal and Connective Tissue Disorders	Any (includes non-CV events)	117 (10.4)	188 (16.1)	304 (13.4)	23 (5.7)	84 (13.1)	23 (5.5)	163 (16.4)	5 (7.8)	204 (14.5)	30 (10.4)	532 (12.6)
	Musculoskeletal chest pain	3 (0.3)	3 (0.3)	6 (0.3)		2 (0.3)		3 (0.3)		3 (0.2)	1 (0.3)	9 (0.2)
General disorders and administration site conditions	Any (includes non-CV events)	99 (8.8)	97 (8.3)	195 (8.6)	36 (9.0)	64 (10.0)	28 (6.7)	132 (13.3)	5 (7.8)	199 (14.1)	50 (17.4)	514 (12.2)

Table 7.1.3.3.1.5.2.1: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO	AC	All Comp	Liraglutide (mg)							
					<0.6	0.6	>0.6-<1.2	1.2	>1.2-<1.8	1.8	>1.8	All LGT
		N= 1122 n(%)	N= 1165 n(%)	N= 2272 n(%)	N= 401 n(%)	N= 641 n(%)	N= 416 n(%)	N= 993 n(%)	N= 64 n(%)	N= 1408 n(%)	N= 288 n(%)	N= 4211 n(%)
	Edema peripheral	19 (1.7)	19 (1.6)	38 (1.7)		3 (0.5)	1 (0.2)	16 (1.6)		12 (0.9)	2 (0.7	34 (0.8)
	Chest pain	7 (0.6)	12 (1.0)	19 (0.8)	1 (0.2)		2 (0.5)	7 (0.7)		7 (0.5)		17 (0.4)
	Chest discomfort	2 (0.2)		2 (0.1)			2 (0.5)	5 (0.5)		1 (0.1)		8 (0.2)
	Edema		3 (0.3)	3 (0.1)	1 (0.2)	3 (0.5)		1 (0.1)		1 (0.1)		6 (0.1)
	Noncardiac chest pain	1 (0.1)	1 (0.1)	2 (0.1)				1 (0.1)		2 (0.1)		3 (0.1)
	Gravitational edema	2 (0.2)		2 (0.1)	1 (0.2)			1 (0.1)				2 (<0.1)
	Pitting edema		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)
	Generalized edema		1 (0.1)	1 (<0.1)	1 (0.2)			1 (0.1)				2 (<0.1)
	Local swelling		1 (0.1)	1 (<0.1)		1 (0.2)						1 (<0.1)
	Swelling		1 (0.1)	1 (<0.1)								
Metabolism and nutrition disorders	Any (includes non-CV events)	75 (6.7)	81 (7.0)	156 (6.9)	24 (6.0)	47 (7.3)	10 (2.4)	145 (14.6)	1 (1.6)	230 (16.3)	26 (9.0)	483 (11.5)
	Fluid retention		3 (0.3)	3 (0.1)				3 (0.3)		3 (0.2)		6 (0.1)
Respiratory, thoracic and mediastinal disorders	Any (includes non-CV events)	61 (5.4)	76 (6.5)	137 (6.0)	20 (5.0)	40 (6.2)	15 (3.6)	75 (7.6)	3 (4.7)	90 (6.4)	9 (3.1)	252 (6.0)
	Dyspnea	2 (0.2)	4 (0.3)	6 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	5 (0.5)	1 (1.6)	5 (0.4)		14 (0.3)
	Pulmonary embolism	1 (0.1)		1 (<0.1)				1 (0.1)		1 (0.1)		2 (<0.1)
	Pleural effusion							2 (0.2)				2 (<0.1)
	Pulmonary edema		1 (0.1)	1 (<0.1)								
	Dyspnea exertional							1 (0.1)				1 (<0.1)
Investigations	Any (includes non-CV events)	61 (5.4)	70 (6.0)	131 (5.8)	9 (2.2)	45 (7.0)	3 (0.7)	68 (6.8)		94 (6.7)	8 (2.8)	227 (5.4)
	Blood CPK incr	4 (0.4)	13 (1.1)	17 (0.7)		4 (0.6)		9 (0.9)		10 (0.7)	2 (0.7)	25 (0.6)
	Weight increased	1 (0.1)	13 (1.1)	14 (0.6)	1 (0.2)			3 (0.3)		6 (0.4)		10 (0.2)
	C-reactive protein increased	2 (0.2)	4 (0.3)	6 (0.3)		2 (0.3)		4 (0.4)		3 (0.2)		9 (0.2)
	Blood pressure increased	4 (0.4)	1 (0.1)	5 (0.2)				4 (0.4)		5 (0.4)		9 (0.2)
	ECG abnl	3 (0.3)	3 (0.3)	6 (0.3)	2 (0.5)	3 (0.5)		1 (0.1)		1 (0.1)		7 (0.2)
	Plasminogen activator inhibitor increased	1 (0.1)	1 (0.1)	2 (0.1)		5 (0.8)		3 (0.3)		1 (0.1)		9 (0.2)

Table 7.1.3.3.1.5.2.1: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Blood cholesterol increased	2 (0.2)	1 (0.1)	3 (0.1)		1 (0.2)		1 (0.1)		2 (0.1)		4 (0.1)
	Heart rate increased	1 (0.1)		1 (<0.1)		1 (0.2)		2 (0.2)		2 (0.1)		5 (0.1)
	Cardiac murmur	1 (0.1)		1 (<0.1)				3 (0.3)				3 (0.1)
	LDL incr	1 (0.1)	1 (0.1)	2 (0.1)						1 (0.1)		1 (<0.1)
	Brain natriuretic peptide increased		1 (0.1)	1 (<0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	ECG QT prolonged									2 (0.1)		2 (<0.1)
	ECG change		1 (0.1)	1 (<0.1)		1 (0.2)						1 (<0.1)
	Carotid bruit	1 (0.1)		1 (<0.1)				1 (0.1)				1 (<0.1)
	Blood CPK abnl	1 (0.1)		1 (<0.1)		1 (0.2)						1 (<0.1)
	VLDL incr					1 (0.2)						1 (<0.1)
	QRS axis abnl									1 (0.1)		1 (<0.1)
	Pulse absent									1 (0.1)		1 (<0.1)
	Pulse abnl					1 (0.2)						1 (<0.1)
	Lipids increased		1 (0.1)	1 (<0.1)								
	HDL decreased	1 (0.1)		1 (<0.1)								
	Heart sounds abnl									1 (0.1)		1 (<0.1)
	Heart rate irregular	1 (0.1)		1 (<0.1)								
	Heart rate decreased		1 (0.1)	1 (<0.1)								
	Free fatty acids incr				1 (0.2)							1 (<0.1)
	ECG T wave abnl				1 (0.2)							1 (<0.1)
	ECG ST-T change	1 (0.1)		1 (<0.1)								
	ECG Q wave abnl									1 (0.1)		1 (<0.1)
	ECG signs of myocardial ischemia	1 (0.1)		1 (<0.1)								
	Atrial natriuretic peptide incr		1 (0.1)	1 (<0.1)								
Surgical and medical procedures	Any (includes non-CV events)	3 (0.3)	9 (0.8)	12 (0.5)		4 (0.6)		8 (0.8)		5 (0.4)	1 (0.3)	18 (0.4)
	Coronary artery stent insertion	1 (0.1)		1 (<0.1)								

Table 7.1.3.3.1.5.2.1: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO	AC	All Comp	Liraglutide (mg)							
					<0.6	0.6	>0.6-<1.2	1.2	>1.2-<1.8	1.8	>1.8	All LGT
		N= 1122 n(%)	N= 1165 n(%)	N= 2272 n(%)	N= 401 n(%)	N= 641 n(%)	N= 416 n(%)	N= 993 n(%)	N= 64 n(%)	N= 1408 n(%)	N= 288 n(%)	N= 4211 n(%)

Source: NDA 22341, submission stamp date 16 Jan 2009
Abbreviations: AC = active control, AV = atrioventricular, CPK = creatine phosphokinase, CV = cardiovascular, CVA = cerebrovascular accident, ECG = electrocardiogram, incr = increased, LDL = low density lipoprotein cholesterol, PBO = placebo, TIA = transient ischemic attack, VLDL = very low density lipoprotein cholesterol

Among the events in the above table, few occurred with higher frequency among liraglutide-treated patients than among comparator-treated patients. However, it should be noted that the pooled safety database is somewhat different from the database used to compare the incidence of MACE events in liraglutide versus active comparator and liraglutide versus placebo comparator groups. This is because the MACE analyses that Dr. Derr and Novo conducted were stratified, and involved only those studies with the pertinent comparator.

The following table includes those events that occurred in at least 3 liraglutide-treated patients, and which occurred with a frequency ≥0.2% higher in a liraglutide group than in a comparator group.

Table 7.1.3.3.1.5.2.2: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) Which Occurred in at Least 3 Liraglutide-treated Patients and Occurred With a Numerically Higher (≥0.2% Higher) Frequency in a Liraglutide Group than in a Comparator Group, by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO	AC	All Comp	Liraglutide (mg)							
					<0.6	0.6	>0.6-<1.2	1.2	>1.2-<1.8	1.8	>1.8	All LGT
		N= 1122 n(%)	N= 1165 n(%)	N= 2272 n(%)	N= 401 n(%)	N= 641 n(%)	N= 416 n(%)	N= 993 n(%)	N= 64 n(%)	N= 1408 n(%)	N= 288 n(%)	N= 4211 n(%)
Cardiac	Any	25 (2.2)	32 (2.7)	57 (2.5)	6 (1.5)	31 (4.8)	3 (0.7)	46 (4.6)	2 (3.1)	45 (3.2)	6 (2.1)	139 (3.3)
	Palpitations	4 (0.4)	5 (0.4)	9 (0.4)	2 (0.5)	2 (0.3)		6 (0.6)		12 (0.9)	5 (1.7)	27 (0.6)
	Angina pectoris	3 (0.3)	3 (0.3)	6 (0.3)		9 (1.4)	1 (0.2)	5 (0.5)	1 (1.6)	4 (0.3)		20 (0.5)
	Tachycardia	2 (0.2)	3 (0.3)	5 (0.2)	2 (0.5)	2 (0.3)		5 (0.5)		4 (0.3)		13 (0.3)
	Ventricular extrasystoles	1 (0.1)	2 (0.2)	3 (0.1)		1 (0.2)		3 (0.3)		4 (0.3)		8 (0.2)
	Myocardial ischemia	1 (0.1)		1 (<0.1)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.3)	1 (1.6)	2 (0.1)		9 (0.2)
	Atrial fibrillation		3 (0.3)	3 (0.1)		1 (0.2)				3 (0.2)	1 (0.3)	5 (0.1)
	Coronary artery disease		1 (0.1)	1 (<0.1)		1 (0.2)		2 (0.2)		3 (0.2)		6 (0.1)

Table 7.1.3.3.1.5.2.2: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) Which Occurred in at Least 3 Liraglutide-treated Patients and Occurred With a Numerically Higher (≥0.2% Higher) Frequency in a Liraglutide Group than in a Comparator Group, by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Bundle branch block right							1 (0.1)		4 (0.3)		5 (0.1)
Vascular	Any	26 (2.3)	57 (4.9)	83 (3.7)	9 (2.2)	31 (4.8)	11 (2.6)	42 (4.2)	1 (1.6)	56 (4.0)	10 (3.5)	160 (3.8)
	Hypertension	15 (1.3)	40 (3.4)	55 (2.4)	5 (1.2)	15 (2.3)	1 (0.2)	21 (2.1)	1 (1.6)	30 (2.1)	1 (0.3)	74 (1.8)
	Vascular calcification	1 (0.1)	4 (0.3)	5 (0.2)		6 (0.9)		3 (0.3)		6 (0.4)	2 (0.7)	17 (0.4)
	Hematoma	3 (0.3)	2 (0.2)	5 (0.2)		4 (0.6)		1 (0.1)		4 (0.3)		9 (0.2)
	Hypotension		2 (0.2)	2 (0.1)			1 (0.2)	6 (0.6)		3 (0.2)	2 (0.7)	12 (0.3)
	Flushing	1 (0.1)		1 (<0.1)	2 (0.5)		1 (0.2)	2 (0.2)		2 (0.1)	2 (0.7)	9 (0.2)
	Hot flush		1 (0.1)	1 (<0.1)			3 (0.7)	1 (0.1)		3 (0.2)		7 (0.2)
	Aortic calcification		3 (0.3)	3 (0.1)		4 (0.6)				1 (0.1)	1 (0.3)	6 (0.1)
	Arteriosclerosis				1 (0.2)	3 (0.5)		1 (0.1)		2 (0.1)		7 (0.2)
	Orthostatic hypotension	1 (0.1)		1 (<0.1)		1 (0.2)		3 (0.3)		1 (0.1)		5 (0.1)
Nervous system	Any (includes non-CV events)	189 (16.8)	184 (15.8)	371 (16.3)	63 (15.7)	90 (14.0)	73 (17.5)	195 (19.6)	12 (18.8)	295 (21.0)	58 (20.1)	786 (18.7)
	Syncope	3 (0.3)	1 (0.1)	4 (0.2)	2 (0.5)	1 (0.2)		1 (0.1)		5 (0.4)	1 (0.3)	10 (0.2)
Musculoskeletal and Connective Tissue Disorders	Any (includes non-CV events)	117 (10.4)	188 (16.1)	304 (13.4)	23 (5.7)	84 (13.1)	23 (5.5)	163 (16.4)	5 (7.8)	204 (14.5)	30 (10.4)	532 (12.6)
General disorders and administration site conditions	Any (includes non-CV events)	99 (8.8)	97 (8.3)	195 (8.6)	36 (9.0)	64 (10.0)	28 (6.7)	132 (13.3)	5 (7.8)	199 (14.1)	50 (17.4)	514 (12.2)
	Chest discomfort	2 (0.2)		2 (0.1)			2 (0.5)	5 (0.5)		1 (0.1)		8 (0.2)
	Edema		3 (0.3)	3 (0.1)	1 (0.2)	3 (0.5)		1 (0.1)		1 (0.1)		6 (0.1)
Metabolism and nutrition disorders	Any (includes non-CV events)	75 (6.7)	81 (7.0)	156 (6.9)	24 (6.0)	47 (7.3)	10 (2.4)	145 (14.6)	1 (1.6)	230 (16.3)	26 (9.0)	483 (11.5)
	Fluid retention		3 (0.3)	3 (0.1)				3 (0.3)		3 (0.2)		6 (0.1)
Respiratory, thoracic and mediastinal disorders	Any (includes non-CV events)	61 (5.4)	76 (6.5)	137 (6.0)	20 (5.0)	40 (6.2)	15 (3.6)	75 (7.6)	3 (4.7)	90 (6.4)	9 (3.1)	252 (6.0)
	Dyspnea	2 (0.2)	4 (0.3)	6 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	5 (0.5)	1 (1.6)	5 (0.4)		14 (0.3)
Investigations	Any (includes non-CV events)	61 (5.4)	70 (6.0)	131 (5.8)	9 (2.2)	45 (7.0)	3 (0.7)	68 (6.8)		94 (6.7)	8 (2.8)	227 (5.4)
	Blood CPK incr	4 (0.4)	13 (1.1)	17 (0.7)		4 (0.6)		9 (0.9)		10 (0.7)	2 (0.7)	25 (0.6)

Table 7.1.3.3.1.5.2.2: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) Which Occurred in at Least 3 Liraglutide-treated Patients and Occurred With a Numerically Higher (≥0.2% Higher) Frequency in a Liraglutide Group than in a Comparator Group, by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Weight increased	1 (0.1)	13 (1.1)	14 (0.6)	1 (0.2)			3 (0.3)		6 (0.4)		10 (0.2)
	C-reactive protein increased	2 (0.2)	4 (0.3)	6 (0.3)		2 (0.3)		4 (0.4)		3 (0.2)		9 (0.2)
	Blood pressure increased	4 (0.4)	1 (0.1)	5 (0.2)				4 (0.4)		5 (0.4)		9 (0.2)
	ECG abnl	3 (0.3)	3 (0.3)	6 (0.3)	2 (0.5)	3 (0.5)		1 (0.1)		1 (0.1)		7 (0.2)
	Plasminogen activator inhibitor increased	1 (0.1)	1 (0.1)	2 (0.1)		5 (0.8)		3 (0.3)		1 (0.1)		9 (0.2)
	Cardiac murmur	1 (0.1)		1 (<0.1)				3 (0.3)				3 (0.1)
Surgical and medical procedures	Any (includes non-CV events)	3 (0.3)	9 (0.8)	12 (0.5)		4 (0.6)		8 (0.8)		5 (0.4)	1 (0.3)	18 (0.4)

Source: NDA 22341, submission stamp date 16 Jan 2009

Overall cardiac and vascular System Organ Class events occurred with slightly numerically higher frequency for the total liraglutide-treated group than for the placebo-treated group, but with similar frequency to the active control and overall comparator group. Overall neurologic System Organ Class events occurred with slightly numerically higher frequency for the total liraglutide-treated group than for comparator groups. However, it should be noted that the pooled safety database is somewhat different from the database used to compare the incidence of MACE events in liraglutide versus active comparator and liraglutide versus placebo comparator groups. This is because the MACE analyses that Dr. Derr and Novo conducted were stratified, and involved only those studies with the pertinent comparator.

The terms "hypotension" and "orthostatic hypotension" occurred with slightly numerically higher frequency among liraglutide-treated patients than among comparator-treated patients. "Hypotension" occurred in 12 (0.3%) of liraglutide-treated patients and in 2 (0.1%) of comparator-treated patients. "Orthostatic hypotension" occurred in 5 (1%) of liraglutide-treated patients and in 1 (<0.1%) of comparator-treated patients. Other slight numerical imbalances of note include the terms "angina pectoris" (LGT n=20 [0.5%] versus comp n=6 [0.3%]) and "myocardial ischemia" (LGT n=9 [0.2%] versus comp n=1 [<0.1%]). The slightly higher incidence of the terms "flushing" and "hot flush" is potentially of some interest to the later discussion of thyroid cancer, because medullary thyroid carcinoma is a rare entity in the differential diagnosis of flushing (Izikson 2006). Other causes of flushing are much more

common, however. The overall incidence of each of the event terms discussed in this paragraph was low.

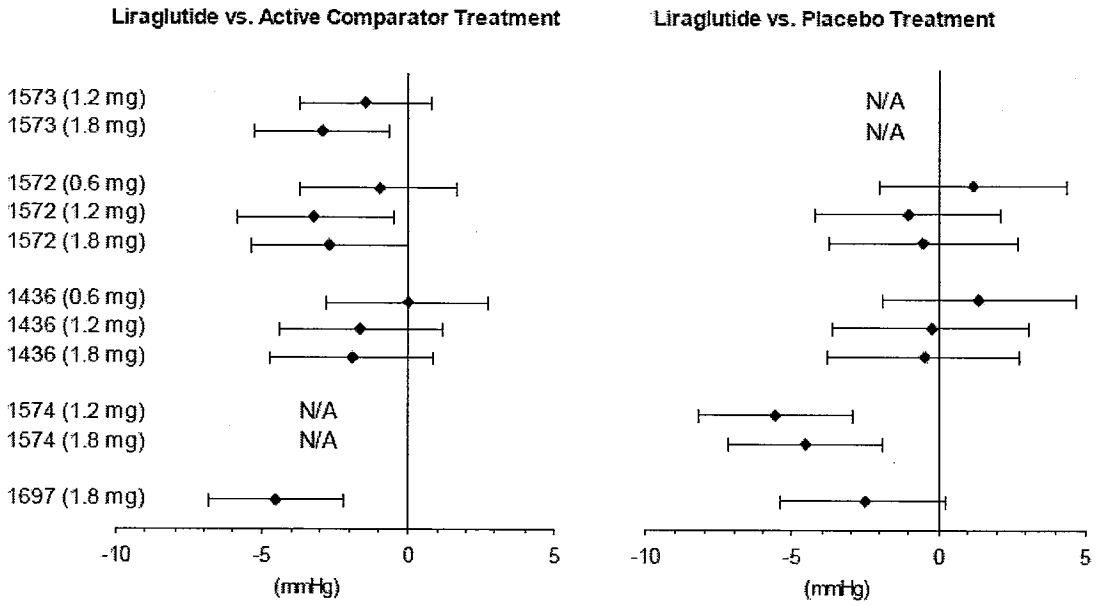
Otherwise, within each of these System Organ Classes, no particular potential cardiovascular event term appeared to show an unfavorable imbalance for liraglutide. Imbalances were not noted for dysrhythmias or cardiac failure events.

7.1.3.3.1.6: Changes From Baseline in Cardiovascular Risk Factors

Changes from baseline in cardiovascular risk factors (blood pressure, lipids, C-reactive protein et al) were efficacy endpoints. The review of clinical efficacy is being conducted by Dr. Yanoff, and is ongoing. The following sections summarize the applicant's statements regarding changes in these risk factors.

In the five major Phase 3 trials, liraglutide did not increase systolic blood pressure; most point estimates for liraglutide versus comparator favored liraglutide, particularly for comparisons to other active antidiabetic agents. The following figure displays point estimates and confidence intervals for change in systolic blood pressure.

Figure 7.1.3.3.1.6.1. Change from Baseline in Systolic Blood Pressure, Liraglutide versus Comparator, Five Major Phase 3 Trials



Source: Applicant's Figure 3-8, Summary of Clinical Efficacy, pg 117
Time period is from baseline to time of measurement of primary HbA1c efficacy endpoint

The applicant reports that there was no significant effect of liraglutide on diastolic blood pressure in the Phase 3 trials.

Liraglutide was associated with a small but statistically significant increase in heart rate in the five major Phase 3 trials, as illustrated in the following repeated measurements analysis by the applicant.

Table 7.1.3.3.1.6.1: Repeated Measurements Analysis (by Novo) of Heart Rate (Beats per Minute), Five Major Phase 3 Trials

Comparison of levels in Pulse after 26/28, 52 and 76/78 weeks of treatment

Treatment / Comparison	Estimates			P-value
Week 26/28				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	1053	77.55	(0.31)	
Liraglutide 1.2mg	805	77.14	(0.34)	
Liraglutide 0.6mg	471	77.73	(0.40)	
Active Comparator	851	75.82	(0.31)	
Placebo	501	75.03	(0.41)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	1.73	[1.01 ;	2.45]	<.0001
Lira 1.2 vs. Active	1.32	[0.55 ;	2.09]	0.0008
Lira 0.6 vs. Active	1.91	[1.01 ;	2.82]	<.0001
Lira 1.8 vs. Placebo	2.52	[1.67 ;	3.37]	<.0001
Lira 1.2 vs. Placebo	2.11	[1.22 ;	3.00]	<.0001
Lira 0.6 vs. Placebo	2.70	[1.69 ;	3.72]	<.0001
Week 52				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	389	76.84	(0.41)	
Liraglutide 1.2mg	392	77.11	(0.41)	
Liraglutide 0.6mg	173	77.27	(0.57)	
Active Comparator	394	74.94	(0.40)	
Placebo	52	74.38	(0.98)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	1.90	[0.88 ;	2.91]	0.0002
Lira 1.2 vs. Active	2.17	[1.15 ;	3.19]	<.0001
Lira 0.6 vs. Active	2.33	[1.03 ;	3.63]	0.0004
Lira 1.8 vs. Placebo	2.46	[0.44 ;	4.47]	0.0167
Lira 1.2 vs. Placebo	2.73	[0.71 ;	4.75]	0.0080
Lira 0.6 vs. Placebo	2.89	[0.72 ;	5.05]	0.0089
Week 76/78				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	180	76.58	(0.54)	
Liraglutide 1.2mg	194	77.16	(0.53)	
Liraglutide 0.6mg	105	77.49	(0.70)	
Active Comparator	161	75.89	(0.57)	
Placebo	22	74.69	(1.44)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	0.69	[-0.77 ;	2.16]	0.3529
Lira 1.2 vs. Active	1.27	[-0.18 ;	2.72]	0.0851
Lira 0.6 vs. Active	1.61	[-0.10 ;	3.32]	0.0655
Lira 1.8 vs. Placebo	1.89	[-1.09 ;	4.86]	0.2135
Lira 1.2 vs. Placebo	2.46	[-0.50 ;	5.43]	0.1034
Lira 0.6 vs. Placebo	2.80	[-0.30 ;	5.90]	0.0766

The estimates are from an repeated measurement model with country, previous treatment, treatment, time, treatment by time as fixed effects and baseline pulse level as a covariate and subject as random effect
For complete treatment regimens in the individual trials, see Table 1-1

Cross-reference: Appendix 7.2, Table 243.

Source: Applicant's Table 4-1, Integrated Summary of Safety, pg 203

In general, liraglutide was not associated with significant changes in serum lipids versus comparator agents. The following table by the applicant displays liraglutide's effect on lipids in the Phase 3 trials. For each trial, and for each lipid category, the table denotes whether liraglutide had no effect (O), had a statistically significant favorable effect (S), or had a statistically significant undesirable effect (I).

Table 7.1.3.3.1.6.2: Effect of Liraglutide on Serum Lipid Parameters, Five Major Phase 3 Trials, Analyses by Novo

Trial ID	Weeks from Baseline	Treatment	FFA	LDL-C	TC	VLDL-C	TG	HDL-C	ApoB
Therapeutic Confirmatory Trials									
1573	52 weeks	Lira							
		vs. Glim	S	O	O	O	O	O	O
1572	26 weeks	Lira+Met							
		vs. Pla+Met	O	O	O	S	S	O	O
		vs. Glim+Met	O	O	O	O	O	O	O
1436	26 weeks	Lira+Glim							
		vs. Pla+Glim	O	O	S	O	O	O	O
		vs. Rosi+Glim	O	S	S	S	O	I	O
1574	26 weeks	Lira+Met+Rosi							
		vs. Pla+Met+Rosi	S	S	O	O	S	O	N/A
1697	26 weeks	Lira+Met+Glim							
		vs. Pla+Met+Glim	S	O	O	O	O	O	O
		vs. Iglar+Met+Glim	O	S	S	O	O	O	O
Therapeutic Exploratory Trials									
1571	14 weeks	Lira							
		vs. Pla	O	I	O	O	S	O	O
1333		Lira							
	1 week	vs. Pla	O	O	S	N/A	O	O	N/A
	8 weeks	vs. Pla	O	O	O	N/A	O	O	N/A
Japanese trial									
1334	14 weeks	Lira							
		vs. Pla	O	O	O	O	O	O	O

S: liraglutide statistically significantly superior
I: liraglutide statistically significantly inferior
O: no difference
N/A: not assessed
Glim: glimepiride, Iglar: insulin glargine, Lira: liraglutide, Met: metformin, Pla: placebo, Rosi: rosiglitazone.

Source: Applicant's Table 3-20, pg 119, Integrated Summary of Efficacy

Liraglutide had no significant effect on change from baseline in levels of hsCRP (highly sensitive C-reactive protein) in the applicant's analyses.

7.1.3.3.1.7: Advisory Committee Discussion Regarding Major Adverse Cardiovascular Events

Please see Section 8.5 for an expanded summary of the Advisory Committee discussion regarding major adverse cardiovascular event data. In the Advisory Committee meeting, data regarding major adverse cardiovascular events were presented to the panel, which included two cardiologists and a biostatistician, in addition to endocrinologists, an epidemiologist, a patient representative and a consumer representative. The panel's overall vote was 8 "yes" and 5 "no" regarding whether the applicant had ruled out an unacceptable increase in cardiovascular risk.

However, both cardiologists and the biostatistician voted "no", citing concerns about small numbers of events, the low cardiovascular risk of the study population, and the difference in results for analyses versus placebo. Other panel members, including some who voted "yes", also expressed concerns about the adequacy of the data.

7.1.3.3.1.8: Summary of Observations Regarding Major Adverse Cardiovascular Events

- The liraglutide development program was not prospectively designed to permit a systematic evaluation of cardiovascular events.
- Few major cardiovascular events occurred across the development program, significantly limiting the ability to assess cardiovascular risk. For time period Population A (considered the most relevant population) and the FDA Custom Endpoint (intended to include events most likely to represent actual MACE events), there were only 26 events, only 23 of which met the regulatory definition of a serious adverse event.
- Cardiovascular events did not undergo pre-planned adjudication, and adequate data were not available for *post hoc* adjudication.
- The development program was not designed to include a large number of patients at high risk of cardiovascular events. In fact, intermediate and longterm trials had an exclusion criterion for patients with significant cardiovascular disease, and thus a high incidence of cardiovascular events would not be expected among the population studied in the development program.
- The development program was not designed to facilitate the combination of its trials into a meta-analysis. Trials were of varying durations, and the blinded and open-label periods differed among major Phase 3 trials.
- Choice of endpoint, comparator, and analysis method altered some results of cardiovascular event analyses.
- In general, when comparing liraglutide to overall pooled comparator (placebo and active comparator) for risk of major adverse cardiovascular events (cardiovascular death, myocardial infarction or stroke based on the Broad and Custom MACE endpoints), using analysis methods stratified by study, the point estimates were <1, and 95% confidence intervals included 1. The upper bound of the 95% confidence interval usually exceeded 1.3. The estimates were not very sensitive to choice of estimation methodology.
- Comparisons of liraglutide to active comparator for MACE were qualitatively similar to comparisons of liraglutide to total comparator. The estimates were somewhat sensitive to choice of estimation methodology.
- Comparisons of liraglutide to placebo for MACE sometimes resulted in a point estimate >1 (not favoring liraglutide), with the confidence intervals including 1, and an upper bound of the 95% confidence interval >1.8, depending on analysis method. Patients in placebo groups were not at lower cardiovascular risk than patients in other treatment groups, and thus lower risk was not an explanation. Estimates were sensitive to choice of estimation methodology. Low event rates among placebo-treated patients (and low event rates in general) are likely to have contributed to the sensitivity to methodology.
- There did not appear to be a relationship between liraglutide dose and risk of a major adverse cardiovascular event.
- When considering all adverse events that were possibly cardiovascular in nature (not limited to cardiovascular death, stroke or myocardial infarction), there were few events or groups of

events which appeared to occur with higher frequency among liraglutide-treated patients than among comparator-treated patients. Overall MedDRA System Organ Class events for the Cardiac Disorders and Vascular Disorders System Organ Classes (SOCs) occurred with slightly numerically higher frequency for liraglutide-treated patients than for placebo-treated patients, but with similar frequency for liraglutide versus active comparator and liraglutide versus overall comparator. These were observations of pooled data, and not stratified analyses.

- There were slightly numerically more patients who had events of "hypotension", "angina pectoris" and "myocardial ischemia" in the overall liraglutide group than in the overall comparator group, but the overall incidence of these individual event terms was low. These were observations of pooled data, and not stratified analyses.
- Overall, deaths from any cause occurred at a low rate, and occurred with approximately equal frequency among liraglutide-treated patients and comparator-treated patients.
- At the Advisory Committee meeting, both cardiologists on the Committee, and the biostatistician, voted "no" when asked if the applicant had ruled out an unacceptable increase in cardiovascular risk. The overall vote of the committee was 8 "yes" and 5 "no". Those who voted "no", and some who voted "yes", expressed concerns about the low event rates and the overall adequacy of the data.

7.1.3.3.2 Thyroid Cancer and Calcitonin

7.1.3.3.2.1. Introduction to the Review of Thyroid Cancer and Calcitonin

In 2-year lifetime exposure carcinogenicity studies in mice and rats, liraglutide caused thyroid C-cell tumors in both species, in both genders, at clinically relevant exposures. In rats, C-cell carcinomas occurred at clinically relevant exposures. In mice, only females developed carcinomas, and only at high multiples of expected human exposure. However, in rodents, C-cell adenomas are considered to be a precarcinomatous lesion. There was a long latent period from first exposure to development of C-cell tumors. A similar animal signal is being noted in interim carcinogenicity data for some other long-acting (q day and longer) GLP-1 analogues in development. In animal studies of liraglutide, calcitonin (which has been used historically as a biomarker for medullary thyroid cancer in humans) may not have been a reliable biomarker for C-cell tumor risk. Dr. Parola stated that the mechanistic studies performed by the applicant did not mitigate this risk. At this time there are no known FDA-approved drugs that have caused C-cell tumors in two species; it is not known if a drug with this finding has ever been submitted for consideration for approval. Please see Dr. Parola's review for details of the findings of these animal studies.

After a finding of increased carcinogenicity risk in animals, it is sometimes difficult to determine whether that finding translates to increased human risk. There are species differences in susceptibility to certain tumors, and there are other differences between rodents and humans which may be relevant. Dr. Parola's review addresses these relevant differences. The clinical review sought to determine whether medullary thyroid cancer occurred in any patients, whether other types of thyroid cancer occurred, and whether potential precancerous signs of medullary thyroid carcinoma, e.g. hypercalcitoninemia or C-cell hyperplasia, occurred.

Medullary thyroid cancer (MTC) is a relatively rare form of thyroid cancer, accounting for only about 5% of all thyroid carcinomas in the United States (Hundahl 1998). Approximately 600 cases are reported per year in the United States. Medullary carcinoma arises from the C-cells of the thyroid gland. The C-cells normally secrete calcitonin, a hormone which is involved in calcium homeostasis. In medullary thyroid carcinoma, calcitonin is often secreted in excess. Most cases of medullary thyroid carcinoma are sporadic, but familial forms exist, in which medullary thyroid carcinoma is autosomally dominantly inherited, either as the carcinoma alone, or as part of a multiple endocrine neoplasia syndrome. These familial forms of medullary thyroid carcinoma are often associated with mutations in the "rearranged during transfection" (RET) proto-oncogene. Sporadic medullary thyroid carcinoma usually occurs as a single thyroid tumor; familial MTC is often bilateral and multicentric.

In addition to secreting calcitonin, medullary thyroid carcinomas may secrete other substances, including corticotropin, carcinoembryogenic antigen, histamine, and other vasoactive peptides.

Medullary thyroid cancer is usually indolent in terms of rate of growth, although not always. Except in the case of certain RET mutations where MTC can be seen in infancy, both familial and sporadic forms probably take years to grow enough to produce a palpable nodule. Because of this indolence, one might not expect to see cases of MTC over the duration of the typical drug development program, even if the drug was truly capable of causing MTC. Early complete surgical excision is currently the only curative option. Completely resected patients usually go on to die of something other than MTC. The 10-year survival rate of patients with MTC averaged 75% in 1998 (Hundahl 1998), but has probably been improving due to improved early detection and early thyroidectomy for familial forms. However, the outcome for nonresectable cases is much worse, with a median survival of 3.2 years. When complete resection is not possible, palliative treatments are often attempted, but these patients usually have MTC as their cause of death, rather than another cause. Local neck invasion, with asphyxia or other catastrophic local invasive process, is often the cause of death in nonresectable cases.

Survival is strongly linked to tumor stage and patient age (Modigliani 1998). Sporadic MTC tends to present at a later age and more advanced stage than familial MTC (Massoll 2004).

Sporadic cases of MTC usually present as an isolated thyroid nodule or as part of a multinodular goitre, often asymptomatic and of long standing (Massoll 2004). Metastases are often present at diagnosis. The tumor may sometimes have a history of recent rapid growth with hoarseness, dysphagia or dyspnea; or it may present with systemic symptoms of diarrhea, flushing or bone pain. However, most tumors do not have these features of rapid growth or hormonal manifestations.

Most cases of familial thyroid carcinoma are now diagnosed through testing of the kin of patients with known MTC. The multiple endocrine neoplasia 2A (MEN2A) syndrome may also include pheochromocytoma and/or hyperparathyroidism. The MEN2B syndrome includes a Marfanoid habitus and mucosal neuromata, and may include pheochromocytoma and/or ganglineuromata. In the MEN2 syndromes, MTC tends to present at an earlier age than in familial MTC outside an MEN syndrome; in MEN2B, MTC may even present in infancy. Guidelines have been established for identification of familial cases, and the timing of surgical intervention, through

detection of RET proto-oncogene mutations (current predominant method) and measurement of serum calcitonin (Brandi 2001).

Early complete surgical excision through total thyroidectomy and lymph node dissection is essentially the only curative therapy at this point, although external beam radiotherapy may be effective in eradicating small foci of incompletely resected tumor (Hyer 2000, Massoll 2004, Rougier 1983).

To date, there has not been a clearly-described association between a particular drug and known increased risk of human medullary thyroid carcinoma.

7.1.3.3.2.2: Liraglutide and Human Thyroid Cancer

7.1.3.3.2.2.1: Events of Thyroid Cancer

7.1.3.3.2.2.1.1: Medullary Thyroid Cancer

At the time of NDA submission, there had been no cases of medullary thyroid cancer in the development program. During the review period, the applicant submitted a case of medullary thyroid cancer that had occurred in a comparator-treated patient. Patient 770001 was a 61 year old man who had a baseline calcitonin of 1023 ng/L (upper limit of normal 8.4), and thus likely had medullary thyroid cancer at baseline. He was treated with GLIM, MET and insulin glargine (GLAR) for 144 days. Ultrasound showed that the right lobe of the thyroid was "completely filled" by a nodule, with a 3.9 cm maximum diameter. Fine needle aspiration was inconclusive. After study completion, the patient underwent total thyroidectomy, and was found at pathology to have medullary thyroid carcinoma with typical structural features and multiple positive stains. He had extracapsular spread, with endovascular and endolymphatic propagation. As mentioned above, this patient likely had MTC at baseline.

7.1.3.3.2.2.1.2: Papillary Thyroid Cancer

At the time of submission of the NDA, there had been four cases of papillary thyroid cancer among LGT-treated patients and one case among comparator-treated patients. In completed trials, this corresponded to rates of 1.8 and 0.9 events per 1000 patient-years of exposure, respectively. Subsequent to submission of the NDA, two additional cases were reported for liraglutide-treated patients. Using updated exposure data, updated rates would be approximately 2.1 LGT (6 events over 2882 patient-years [PY]) versus 0.7 non-LGT (1 event over 1486 PY).

The following table provides information regarding these seven cases.

Table 7.1.3.3.2.2.1.2: Papillary Thyroid Cancer Cases from the Liraglutide Development Program

Study	Pt ID	Age	Gender	Tx	Exp	Outcome	Tumor Size	Comment
1334	16004	70	f	LGT 0.6	99 d	Thyroid surgery; adjuvant treatment not mentioned; longterm outcome not mentioned	T1 (<2 cm)	
1573	261006	62	f	LGT 1.2	356 d	"	1 mm	Elevated calcitonin preop; C-cell hyperplasia on path
	175008	64	m	LGT 1.8	26 d	"	1 mm	Elevated baseline calcitonin; C-cell hyperplasia on path, "may also be referred to as 'medullary carcinoma *in situ*'"
1436	506001	59	m	LGT 1.8 + GLIM	175 d	"	?	Elevated calcitonin preop
1572	221008	54	m	LGT 1.8 + MET	364 d	"	2 mm	Elevated calcitonin preop; C-cell hyperplasia on path
1574	326016	53	f	LGT 1.8 + MET + RSG	50 d	"	9 mm, 2.5 mm, 1 mm	Elevated calcitonin preop
	326008	59	m	MET + RSG	61 d[1]	"	1 mm	Elevated calcitonin preop

Source: Applicant's Table 2-23 and narratives, Module 2.7.4, beg pg 115
Abbreviations: Exp = duration of exposure to study medication prior to time cancer was noted, f = female, GLIM = glimepiride, ID = patient identification number, LGT = liraglutide, m = male, MET = metformin, Path = pathology results, preop = preoperatively, Pt = patient, RSG = rosiglitazone, Tx = study drug treatment
1 The applicant's table states that the exposure was 1 day, but the clinical safety reviewer calculates 61 days.

Brief narratives of these cases follow:

Patient 16004 was a 70 year old woman with a prior history of goitre who received liraglutide, 0.6 mg/day, for 99 days prior to receiving a diagnosis of papillary thyroid cancer. Two months prior to initiation of LGT, at screening, a thyroid ultrasound revealed a nodule in the inferior right lobe of the thyroid; fine needle aspiration (FNA) was suggestive of adenomatoid goitre. The patient completed planned participation in the trial. At or near the end of the trial, the patient underwent repeat fine needle aspiration twice. One FNA was consistent with papillary thyroid carcinoma, and the other was consistent with benign adenoma. Six weeks after cessation of LGT, the patient underwent "a subtotal removal of the right thyroid and D1 dissection". The applicant's narrative states that the pathological diagnosis was "papillary adenocarcinoma, follicular variant, T1bN0M0, EX0". Consistent with the classification, there was no capsular infiltration and no evidence of metastases. The actual surgical pathology report was not provided; it was requested from the applicant on 27 Oct 2008 and again on 11 Feb 2009. On 25 Feb 2009, the applicant reported that no surgical pathology report beyond the stated description

was available, although the applicant did provide translations (from Japanese) of other medical records related to the patient's evaluation and treatment. These translations did not mention whether the patient was living in Japan at the time when radiation exposure from Hiroshima or Nagasaki might have occurred. The patient was discharged seven days after the surgery; follow-up treatment was not reported.

Patient 261006 was a 63 year old woman who received LGT, 1.2 mg/day, for 356 days prior to receiving diagnoses of papillary thyroid cancer and diffuse C-cell hyperplasia. After about 12 months of LGT exposure, the patient had repeated calcium stimulation tests with high calcitonin results. There were no palpable thyroid nodules or enlargement. About 1 month later, ultrasound showed multinodular goitre, with the right lobe more enlarged than the left. One month later, repeat calcium stimulation test again showed "significantly abnormal level of calcitonin". Two months later, a total thyroidectomy was performed. The surgical pathology report was provided (NDA 22341, receipt date 14 Nov 2008, beg pg 139 of case report). Pathology did not reveal medullary thyroid cancer. There were multiple benign adenomatous nodules and a left-sided 1 mm focus of papillary thyroid carcinoma "confirmed by specific stain for papillary thyroid tumour markers". A specific immunohistochemical stain of C-cells showed evidence of C-cell hyperplasia (>50 cells in a single low power field) in multiple blocks. Margins were free of tumor. Tumor-node-metastasis (TNM) classification was not included in the applicant's narrative. The patient was discharged to home one day after surgery; follow-up treatment was not reported. Eighteen days postoperatively, the patient had RET proto-oncogene mutation testing done on peripheral blood; no mutations characteristic of familial forms of medullary thyroid cancer were detected. It should be noted, however, that, even if liraglutide induced medullary thyroid cancer via a RET-dependent mechanism, one might only see the mutations in tumor tissue, and not in peripheral blood. Testing for RET mutations was not done on the thyroid surgical pathology specimen for this patient (NDA 22341, submission stamp date 25 Jun 2009).

Patient 506001 was a 59 year old man who received LGT, 1.8 mg/day, for 175 days prior to receiving a diagnosis of papillary thyroid cancer. After about 3 months of LGT treatment, the patient had high calcitonin levels. Two months later, nodular goitre was diagnosed. Three months later, "subtotal thyroidectomy (left lobe)" was performed, which revealed papillary thyroid cancer. The actual surgical pathology report was not provided; it was requested from the applicant on 27 Oct 2008 and again on 11 Feb 2009. On 25 Feb 2009, the applicant provided a translation (from Russian) of a surgical note, which stated that the histology was consistent with "nodular colloid goitre and papillary microcarcinoma/cicatricial carcinoma with calcification (left lobe)". The TNM classification was not reported. The translation does not mention whether the patient had lived in an area with radiation exposure related to the Chernobyl nuclear accident. The patient was discharged to home 3 days after surgery. Two months later, I131 body scan showed no extrathyroidal activity, "and a thyroid stimulating hormone blood sample was normal". (Reviewer note: a normal thyroid-stimulating hormone level [TSH] at the time of radioactive [RAI] scanning may be undesirable. Elevated TSH [either endogenous or attained through exogenous administration] is desired to drive the RAI into any remaining thyroid cancer cells so that they are detectable on the scan.) The patient continued LGT, and completed the trial 7 months post-operatively.

Patient 221008 was a 54 year old man who received LGT, 1.8 mg, for 364 days prior to receiving a diagnosis of papillary thyroid cancer and C-cell hyperplasia. After approximately 9 months on LGT, the patient had a calcitonin value of 22.3 ng/L. Six weeks later, thyroid ultrasound revealed multinodular goitre, and on a calcium stimulation test, "calcitonin was stimulable in a highly pathological manner" (peak stimulated value 508 ng/L). He was withdrawn from the study, and subsequently underwent a total thyroidectomy with central lymphadenectomy. Bilateral multinodular goitre was noted, as well as a 2 mm right papillary carcinoma. Immunohistochemical staining was consistent with diffuse C-cell hyperplasia. Postoperatively, serum calcitonin was undetectable. This patient's case report was submitted to IND 61040 on 26 Feb 2009.

Patient 326016 was a 53 year old woman who received LGT, 1.8 mg/day, for 50 days prior to receiving a diagnosis of papillary thyroid carcinoma. Early in the trial, elevated calcitonin levels were noted. Because of this, thyroid ultrasound was done after about 3 weeks of LGT exposure. Multinodular goitre was noted. One month later, subtotal thyroidectomy was performed. The surgical pathology report was provided (NDA 22341, receipt date 14 Nov 2008, beg pg 105 of case report). In the right lobe, there was a 0.9 cm papillary thyroid carcinoma, and three papillary microcarcinomata (two at 1 mm size, one at 2.5 mm size). The margins were free of tumor. There was evidence of nodular goitre and lymphocytic thyroiditis. There is no mention in the surgical pathology report of staining for calcitonin, and no mention of examination of C-cells. One month later, completion total thyroidectomy was performed; there was a 2 mm focus of papillary carcinoma in the left lobe, and evidence of lymphocytic thyroiditis. The TNM classification and follow-up were not reported. Liraglutide was not discontinued.

Patient 326008 was a 59 year old man who appears to have received metformin and rosiglitazone for 61 days prior to receiving a diagnosis of papillary thyroid cancer. The applicant's Table 2-23 on page 115 of Module 2.7.4 states that the duration of therapy at onset was 1 day, but the clinical safety reviewer calculates 61 days. After two months of study drug treatment, the patient had an elevated serum calcitonin (19.4 ng/L, upper limit of normal for assay not mentioned). About six weeks later, thyroid ultrasound showed an enlarged thyroid with left lobe nodules. About one month later, left thyroid lobectomy was performed and pathology revealed papillary thyroid cancer. The surgical pathology report was provided (NDA 22341, receipt date 14 Nov 2008, beg pg 78 of case report). The focus of papillary thyroid carcinoma was in the left lobe and was 1 mm in size. The surgical pathology report specifically states that "No medullary carcinoma is identified". Nodular hyperplasia was noted.

Patient 175008 was a 64 year old man who received liraglutide 1.8 mg for 26 days prior to receiving a diagnosis of papillary thyroid cancer and C-cell hyperplasia. The patient had elevated calcitonin (22.3 ng/L) at baseline. The narrative states that "Though this was considered to be a sign of goitre, the condition was not recorded at baseline. The patient was referred to Primary Care Physician and endocrinologist. Per sponsor request, the patient was withdrawn from the study." The reason for discontinuation was listed as an elevated calcitonin level (NDA 22341 safety update, 23 Sep 2008, pg 62 of CRF), which was listed as occurring on Day 1 of therapy. However, the patient appears to have received liraglutide for 26 days prior to discontinuation. Three days after randomization, thyroid ultrasound showed a small hypoechoic lesion in the left upper pole. After 3.5 more months, the patient underwent thyroidectomy. The

surgical pathology report, and a subsequent confirmatory surgical pathology consultation, were provided (NDA 22341, receipt date 25 Feb 2009, beg pg 8 of submission). The surgical pathology report, and the subsequent confirmatory consultation, give diagnoses of bilateral neoplastic C-cell hyperplasia (as opposed to reactive C-cell hyperplasia) and a microscopic (1 mm) papillary carcinoma in the left lobe. There were numerous perifollicular aggregations of atypical C-cells. These aggregations of C-cells were noted immediately adjacent to small collections of solid cell nests, which the pathologist stated were remnants of the ultimobranchial body which gives rise to C-cells. The consultative pathologist states that neoplastic C-cell hyperplasia may also be referred to as "medullary carcinoma *in situ*". There was a 1 mm focus of papillary carcinoma in the left lobe. There were multiple adenomatoid nodules in both lobes. The patient was discharged one day postoperatively. Five weeks postoperatively, serum calcitonin was reported as normal.

Observations regarding the above cases of papillary thyroid carcinoma include:

- All patients who were diagnosed with papillary thyroid cancer were exposed to study treatment for <1 year.
- Four out of the six cases in liraglutide-treated patients occurred among patients treated with the highest dose of liraglutide, 1.8 mg.
- The comparator-treated patient, and all but one of the liraglutide-treated patients, had elevated calcitonin preoperatively. The patient who did not have an elevated calcitonin preop had a baseline goitre with a dominant nodule.
- All of the patients went to surgery because of calcitonin or ultrasound findings that were done as part of clinical trial monitoring.
- Most of the tumors were small (<1 cm); this raises the question of whether these were incidental papillary microcarcinomata. In the medical literature, the reported incidence of papillary microcarcinomata (<1 cm in size) has been increasing, but a growing consensus is that this is due to increased detection within thyroid pathology specimens (often from surgeries done for reasons other than suspected thyroid cancer), rather than a true rise in the incidence of papillary thyroid cancer (Grodski 2008).
- Three of the six liraglutide-treated patients who had papillary thyroid cancer also had C-cell hyperplasia on pathology. The comparator-treated patient who had papillary thyroid cancer did not have C-cell hyperplasia on pathology. Please see Section 7.1.3.3.2.3 for a discussion of C-cell hyperplasia.
- One liraglutide-treated case had a specific report of neoplastic C-cell hyperplasia, which is sometimes referred to as "medullary carcinoma *in situ*". This patient appears to have had elevated baseline calcitonin.
- None were described to have lymph node involvement or metastases.

Overall, it appears that most of these tumors were incidental papillary microcarcinomata discovered after routine per-protocol calcitonin or ultrasound screening. However, ascertainment "bias" may not fully explain the numerical imbalance in cases between liraglutide and comparator, because patients in all treatment arms underwent screening, and presumably should have had papillary microcarcinomata discovered at the same rate.

There is one approved GLP-1 analogue (Byetta®, exenatide). The agency requested that the sponsor (Amylin Pharmaceuticals) for exenatide provide information on all cases of thyroid

cancer in all clinical trials of exenatide. Amylin responded on 19 Dec 2008; as of 30 Sep 2008, there had been no cases of thyroid cancer in clinical trials of Byetta®, which have included >5500 subjects and >4600 subject-years of exposure. Calcitonin was not measured in any of the clinical trials of Byetta®. There had been nine spontaneous postmarketing reports of thyroid cancer (3 papillary and 6 unspecified type); there have been approximately 7 million prescriptions filled for Byetta® with an estimated cumulative exposure of 840,000 patient-years.

7.1.3.3.2.3: Human C-Cell Hyperplasia

In the liraglutide development program, as of 26 Jun 2009, there have been 5 cases of C-cell hyperplasia reported among liraglutide-treated patients, and 1 among comparator-treated patients. These represent approximate rates per 1000 patient-years of 1.7 (5 cases/2882 PY) and 0.7 (1 case/1486 PY), respectively.

The following table summarizes these cases.

Table 7.1.3.3.2.3: C-Cell Hyperplasia Case Features, All Cases Reported as of 26 Jun 2009

ID and Gender	Tx	Exp (days)	BL Static Calcitonin[1] (ng/L)	Preop Static Calcitonin[1] (ng/L)	Preop Stim Calcitonin Pk[2] (ng/L)	Path
228002 m	LGT 0.6	190	21.5	15	142	Diffuse CCH
261006 f	LGT 1.2	484	1.7	4.6	94	Diffuse CCH
221008 m	LGT 1.8	363	15.1	22.3	508	Diffuse CCH
651009 m	LGT 1.2	194	11.6	16.4		Focal CCH
175008 m	LGT 1.8	28	22.3	29.4	?	"MTC *in situ*"
224012 m	MET + GLIM	370	"normal"	12.1	"abnl"	"MTC *in situ*"
1 ULN (ng/L): M = 8.4; F = 5 **2 ULN (ng/L): M = 130; F = 90**						

Brief narratives follow.

Patient 224012 was a 64 year old man who received metformin for 390 days and glimepiride for 370 days. Eight months after discontinuation of these active control drugs, he received a diagnosis of neoplastic C-cell hyperplasia, or medullary carcinoma *in situ*. The patient had a history of struma nodosa (term commonly used in Germany for multinodular goitre), and a normal calcitonin level at baseline. Three months after randomization, he had an elevated calcitonin level of 3.54 pmol/L (ref range upper limit of normal [ULN] 2.46 pmol/L). Calcitonin remained elevated, and the patient had an abnormal pentagastrin stimulation test near the end of study participation. He was eventually referred for surgery, and underwent total thyroidectomy eight months after discontinuation from study. The surgical pathology report was provided (NDA 22341, submission received 14 Nov 2008, pg 112 of submitted case report). This revealed

bilateral nodular goitre. Immunohistochemical staining with antibodies to calcitonin revealed bilateral foci of calcitonin-positive cells, in several cases circumferentially disposed around pre-existing follicles and mostly in small groups. A diagnosis was made of "bilaterally detectable neoplastic-type C-cell hyperplasia (known as medullary carcinoma *in situ*)".

As mentioned in the case reports of papillary thyroid cancer above, Patient 175008, a liraglutide-treated patient, had both papillary thyroid cancer and "medullary carcinoma *in situ*".

On 27 May 2009, the applicant submitted a report to IND 61040 of an additional case of focal C-cell hyperplasia in a liraglutide-treated patient. Patient 651009 was a 52 year old man who received liraglutide 1.2 mg for 194 days. He had a mildly elevated baseline calcitonin of 11.6 ng/L. After 87 days on liraglutide, his serum calcitonin was 22.3 ng/L, and he was referred to a thyroidologist. He was found to have a thyroid nodule which was 6 mm in its largest dimension. Fine needle aspiration was inconclusive. Serum carcinoembryonic antigen level was elevated. The patient underwent screening for pheochromocytoma; testing was negative. During the evaluation period, the patient had a colonoscopy with resection of a polyp, and a subsequent episode of hematochaezia which required hospitalization and resulted in anemia. Eventually, the patient underwent left thyroid lobectomy and isthmusectomy, and was found to have focal C-cell hyperplasia, with aggregates of >50 C-cells each. In animals, focal C-cell hyperplasia is a preneoplastic lesion. There is controversy within the medical literature regarding whether focal C-cell hyperplasia is a preneoplastic lesion in humans.

Patient 228002 was a 59 year old man who received liraglutide 0.6 mg for 190 days prior to receiving a diagnosis of C-cell hyperplasia. He had a mildly elevated baseline calcitonin of 21.5 ng/L. After this was noted, he had an ultrasound which revealed a multinodular goitre. Fine needle aspiration of a dominant (11 mm) nodule yielded only colloid and no cellular material. Pentagastrin stimulation testing yielded a peak stimulated calcitonin value of 142 ng/L. Liraglutide was discontinued, and he underwent thyroidectomy, which revealed bilateral nodular goitre with diffuse C-cell hyperplasia.

Patients 261006 and 221008 are discussed above in the cases of papillary thyroid cancer.

C-cell hyperplasia (CCH) and its pathologic classification are areas of some controversy within endocrinology. C-cell hyperplasia may precede the development of medullary thyroid cancer, but there is controversy regarding the predictive value of this finding in humans. It would be useful to be able to reliably differentiate pathologically between what is termed "reactive" or "physiologic" or "diffuse" CCH, which might not be a preneoplastic lesion, and "focal" or "neoplastic" CCH. Complete resection is probably the only curative option for medullary thyroid carcinoma, and thus accurate early detection of those who are destined to develop it is highly desirable. However, not all individuals with CCH are destined to develop MTC. "Reactive" CCH has been reported in neonates; the elderly; and in patients with hyperparathyroidism, Hashimoto's thyroiditis, and follicular thyroid adenomata (Verga 2007, Guyetant 1994). C-cell hyperplasia is also sometimes seen at autopsy in patients who were not known to have thyroid disease prior to death. The basic pathologic definition for CCH is the presence of an increased number of normal C-cells, typically ≥50 C-cells in at least one low power (100x) field (De Lellis 1981, Albores-Saavedra 2001). Perry (1996) proposed a definition

for neoplastic CCH as that characterized by the presence of large, mildly to moderately atypical, round, polygonal, or spindle-shaped cells with nuclear pleomorphisms. However, there is controversy regarding whether this is a meaningful definition, whether one can truly distinguish between reactive and neoplastic CCH, whether the absence of these pathologic features is truly reassuring, and whether the presence of these features is reliably predictive of malignant potential (Verga 2007, LiVolsi 1997, Hinze 2001, Kaserer 2001). A specific difficulty with regard to interpretation of surgical findings of CCH in the liraglutide program is the fact that much of the pathology literature for CCH was developed from studies of kindreds with known familial MTC. It is unclear whether features of CCH in these kindreds is comparable to CCH (or early MTC) that is possibly induced by a drug.

To date, there have been 5 cases of C-cell hyperplasia reported for liraglutide-treated patients, and 1 for comparator-treated patients. These represent approximate rates per 1000 patient-years of 1.7 (5 cases/2882 PY) and 0.7 (1 case/1486 PY), respectively. The cases in liraglutide-treated patients include the MTC *in situ* and focal CCH cases described previously, as well as 3 additional cases of diffuse CCH that were reported for liraglutide-treated patients. The case in a comparator-treated patient was a case of MTC *in situ*; there were no cases of diffuse CCH reported for comparator-treated patients. All but one of the patients were men. Exposure ranged from 28 to 484 days. All cases were diagnosed through preplanned clinical trial monitoring of calcitonin, and had relatively mild preoperative calcitonin elevations. As with the cases of papillary thyroid carcinoma, the imbalance in cases cannot be entirely explained by ascertainment "bias", because screening occurred in all treatment arms, and therefore incidental findings related to screening would presumably occur at the same rate in both liraglutide-treated and comparator-treated patients. As mentioned above, there is controversy within the medical literature regarding whether CCH is predictive of medullary thyroid carcinoma risk.

7.1.3.3.2.4 Calcitonin

Calcitonin (CT) is a 32 amino acid peptide which is synthesized in mammals in a number of tissues, but the C-cells of the thyroid gland are the primary site of synthesis in humans. It has several known biologic effects. Its most prominent current uses in human medicine are related to its effect of lowering of plasma calcium due to an inhibitory effect on osteoclast-mediated bone resorption, and its role as a tumor marker for medullary thyroid cancer. This latter role is of interest for liraglutide.

In normal humans, circulating levels of calcitonin are very low (<10 pg/mL). Elevation of blood calcium concentration stimulates calcitonin release from C-cells, and low blood calcium levels inhibit calcitonin release. As mentioned earlier, medullary thyroid cancer cells often produce calcitonin in excess. Historically, calcitonin has served as a clinical marker for this malignancy. However, there is a great deal of controversy in the medical literature about the usefulness of calcitonin for screening for medullary thyroid cancer, with several studies suggesting a low positive predictive value for mild calcitonin elevations. Numerous other factors can also cause elevation of calcitonin levels, including smoking (d'Herbomez 2007), chronic renal failure, isolated C-cell hyperplasia in association with lymphocytic thyroiditis or follicular thyroid carcinoma, neuroendocrine tumors (Niccoli 1996), hypergastrinemia (Hadjadj 1997), sepsis (d'Herbomez 2001), acute pancreatitis, burns (Findlay 2004), the use of proton pump inhibitors,

and other conditions. Per Dr. Parola, calcitonin may not have been a reliable biomarker for the liraglutide-associated C-cell tumor findings in animals.

There is perhaps some interplay between glucose metabolism and calcitonin. Intravenous insulin administered to pigs has been shown to increase calcitonin levels, and infusion of insulin directly into surgically-isolated *in situ* pig thyroid gland produced an increase in the secretion rate of calcitonin in thyroid venous effluent blood (Care 1998). Care also demonstrated that intravenous glucose administration raised insulin and calcitonin levels in pigs. Specific binding of radiolabeled insulin has been demonstrated in pig thyroid plasma membranes, and in rat and human medullary thyroid carcinoma C-cells (Care 1998). In rabbit cell models, removal of glucose from the extracellular medium inhibited the normal plateau of calcitonin-induced proton efflux (Santhanagopal 2001); such an effect in humans might result in a feedback-based increase in calcitonin release in response to glucose lowering. In rat liver cells, calcitonin stimulated glycogenolysis and gluconeogenesis (Yamaguchi and Williamson 1983). Addition of calcitonin to isolated rat pancreatic islets inhibited glucose-stimulated insulin release (Alwmark 1986). Administration of calcitonin to healthy humans has been associated with increased blood glucose and decreased blood insulin (Young 1995, Passariello 1989, Giugliano 1984, Petralito 1979) in some studies. Administration of calcitonin during oral glucose tolerance testing in healthy humans, and humans with impaired baseline glucose tolerance, showed an impairment of glucose tolerance with inhibition of glucose-induced insulin secretion and reduction of glucose-mediated glucagon suppression (Passariello 1981). In other studies, however, calcitonin administration resulted in no change in blood glucose, but still caused a fall in serum insulin (Stevenson 1985). The increased serum glucose noted with acute calcitonin administration may not be sustained with chronic administration (Giugliano 1982). The effects of other specific diabetes drugs (other than insulin) on calcitonin levels has not been well-described.

In humans with poorly controlled type 2 diabetes mellitus (Gregorio 1994), and in prepubertal children with type 1 diabetes mellitus (Verrotti 1988), serum calcitonin levels were normal. Human diabetic ketoacidosis, which is associated with insulin deficiency, was not associated with a change in calcitonin level in one study (Topaloglu 2005).

Several researchers have noted homology in amino acid sequences for the A-chain of insulin, calcitonin, the calcitonin-gene-related peptides, and amylin, suggesting that these are part of a superfamily of biologically active peptides (Cooper 1989).

Thus, although data are not entirely consistent, it appears that calcitonin can increase glucose levels in humans, and conversely, that glucose lowering or insulin elevation can increase calcitonin release. Liraglutide stimulates glucose-dependent insulin release, and therefore could have some effect on calcitonin levels which could be independent of a neoplastic effect on C-cells. However, some other antidiabetic agents, such as sulfonylureas, also increase insulin levels, and might also be expected to have a stimulatory effect on calcitonin release.

Routine measurement of calcitonin in all patients presenting with thyroid nodules has been advocated (Elisei 2008), with the rationale that the only curative treatment for medullary thyroid carcinoma is early surgical resection, and that serum calcitonin measurement is more sensitive than fine needle aspiration cytology in detecting MTC. In one analysis, measurement of serum

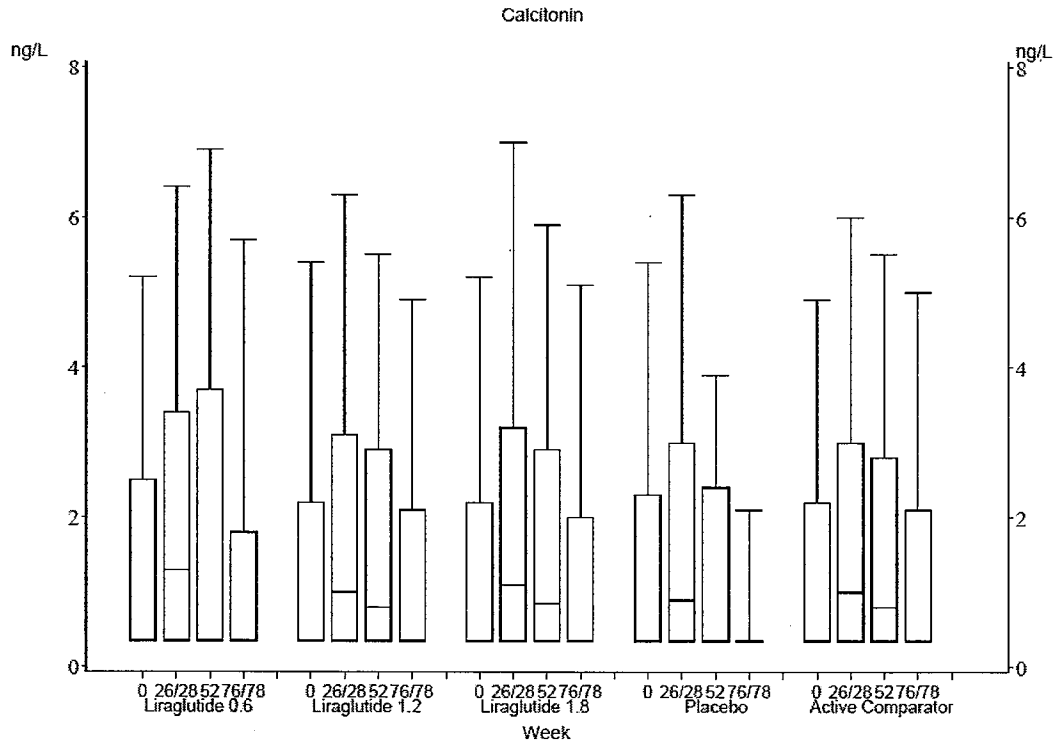
calcitonin in the evaluation of thyroid nodules appeared to be comparably cost-effective to other cancer screening procedures such as colonoscopy and mammography (Cheung 2008). However, in the United States, serum calcitonin is not always measured in the routine evaluation of thyroid nodules, and published consensus guidelines do not yet advocate this routine measurement.

No one has experience in using calcitonin to screen for a possible drug-induced medullary thyroid cancer; calcitonin was mostly used historically to screen family members of patients with known medullary thyroid cancer, prior to the wide availability of RET mutation testing.

The applicant measured calcitonin in the five major Phase 3 clinical trials, and in one single-dose, three short-term and three intermediate-term trials. The applicant also performed calcium stimulation tests on a subpopulation of patients from two trials. The calcitonin assay used had a lower limit of quantification (LLOQ) of 0.7 ng/L. Values below the LLOQ were imputed as 0.35 ng/L. The upper limit of normal for the assay was 5.0 ng/L for women and 8.4 ng/L for men. The clinical review concentrated on data from the five major Phase 3 trials (Studies 1436, 1572, 1573, 1574 and 1697), for which more extensive analyses were available.

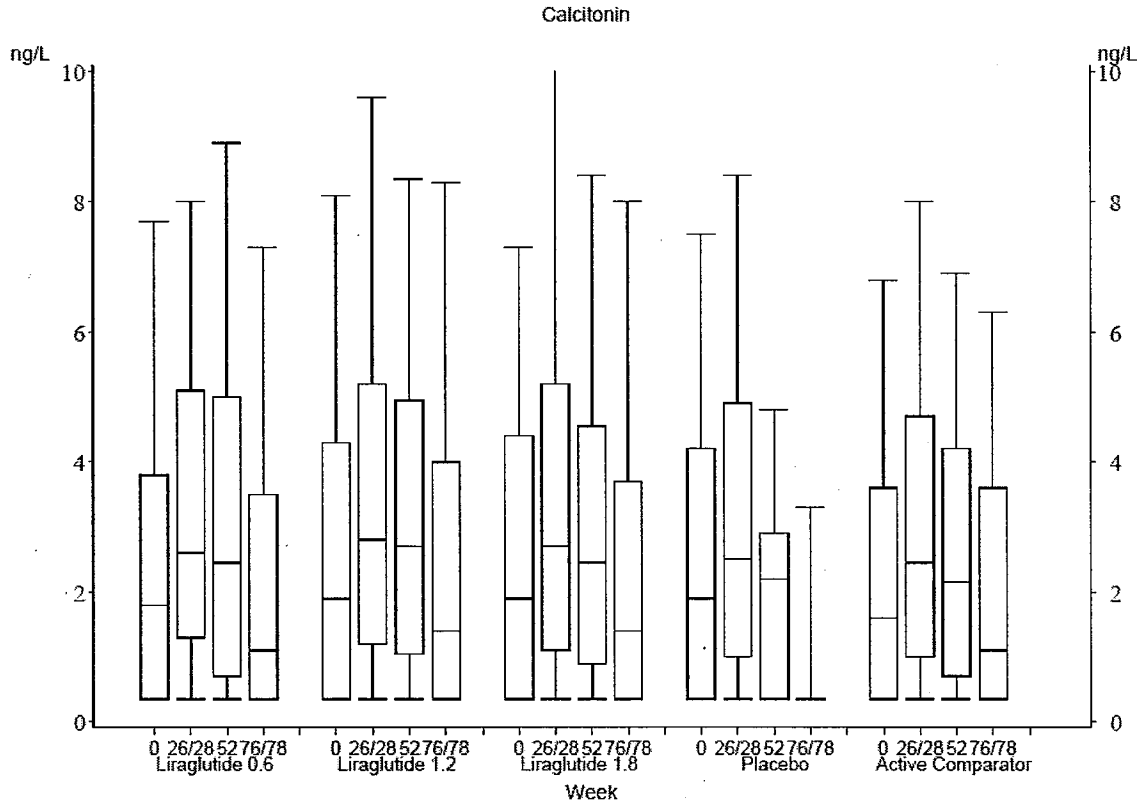
The following box plots present mean and other percentile data for women and men. Visual interpretation of the plots is somewhat complicated by the fact that 85% of women and 30% of men had baseline calcitonin levels below the LLOQ at baseline, and many had values below the LLOQ at other times also. For each box plot, the topmost horizontal line represents the 90^{th} percentile; and the upper limit of the box represents the 75^{th} percentile. If a box has a horizontal line within the box, that line represents the 50^{th} percentile; if a box has no horizontal line within the box, the 50^{th} percentile was at or below the LLOQ. The lower limit of the box represents the 25^{th} percentile. If there is a horizontal line below the lower limit of the box, that line represents the 10^{th} percentile; if there is no horizontal line below the lower limit of the box, the 10^{th} percentile was at or below the LLOQ.

Figure 7.1.3.3.2.4.1: Box Plots for Calcitonin Values for Women, Five Major Phase 3 Trials



Source: Applicant's Figure 3-1, pg 176, ISS, Module 2.7.4

Figure 7.1.3.3.2.4.2: Box Plots for Calcitonin Values for Men, Five Major Phase 3 Trials



Source: Applicant's Figure 3-2, pg 177, ISS, Module 2.7.4

At baseline, calcitonin levels were comparable across treatment groups. As expected, women tended to have lower baseline calcitonin levels than men had. The treatment duration was 26 weeks for Studies 1572, 1436, 1574 and 1697, and 28 weeks for Study 1573. At 26-28 weeks, mean calcitonin levels went up in all treatment groups for both genders, and this increase did not differ significantly between groups when all trials were grouped, as in these figures. Mean values at subsequent time points trended toward lower values compared to the 26-28 week timepoints, and did not differ significantly between treatment groups.

The following tables show the percentages of patients whose calcitonin values shifted from baseline at given time points.

The table below shows the percentages of patients with calcitonin shifts from baseline to weeks 26-28 of treatment for the five major Phase 3 trials. This span of time likely includes the most interpretable data, because trials were randomized and blinded to this point, and subsequent timepoints include some voluntary unblinded extension data, with the potential for confounding.

Table 7.1.3.3.2.4.1: Percentages of Patients with Calcitonin Shifts, Baseline to Weeks 26-28 of Treatment, LOCF, Five Major Phase 3 Trials

		Both sexes Endpoint After 26/28 weeks					Female Endpoint After 26/28 weeks					Male Endpoint After 26/28 weeks				
	Baseline	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤
Liraglutide 0.6mg	1 <LLOQ	34.5	13.7	-	-	1.1	65.8	15.6	-	-	2.0	12.0	12.3	-	-	0.4
	2 LLOQ-UNR	0.6	35.4	2.1	-	0.2	1.0	7.5	1.0	-	-	0.4	55.4	2.9	-	0.4
	3 >UNR-2*UNR	-	0.6	2.1	1.5	-	-	-	1.0	0.5	-	-	1.1	2.9	2.2	-
	4 >2*UNR	-	-	0.4	0.2	-	-	-	-	-	-	-	-	0.7	0.4	-
	5 Missing	0.8	4.2	0.2	-	2.3	1.0	2.0	-	-	2.5	0.7	5.8	0.4	-	2.2
Liraglutide 1.2mg	1 <LLOQ	37.8	14.1	0.1	-	0.2	63.7	16.8	0.2	-	0.2	12.2	11.3	-	-	0.2
	2 LLOQ-UNR	0.4	32.0	1.8	0.1	0.3	0.4	10.5	-	-	-	0.4	53.3	3.6	0.2	0.7
	3 >UNR-2*UNR	0.1	0.6	2.7	0.1	-	0.2	0.2	0.4	0.2	-	-	0.9	4.9	-	-
	4 >2*UNR	-	0.1	0.3	1.1	-	-	-	-	0.2	-	-	0.2	0.7	2.0	-
	5 Missing	1.5	2.3	0.1	-	4.1	2.7	0.9	-	-	3.1	0.2	3.8	0.2	-	5.1
Liraglutide 1.8mg	1 <LLOQ	34.1	15.7	-	-	0.4	59.5	19.2	-	-	0.6	11.9	12.6	-	-	0.3
	2 LLOQ-UNR	1.4	31.4	3.5	-	0.2	0.8	8.9	0.8	-	-	2.0	51.0	6.0	-	0.3
	3 >UNR-2*UNR	-	0.3	1.9	0.8	-	-	-	0.6	-	-	-	0.5	3.0	1.5	-
	4 >2*UNR	0.1	0.1	0.1	0.5	-	0.2	-	-	-	-	-	0.2	0.2	1.0	-
	5 Missing	1.8	3.1	0.5	0.2	4.0	3.2	1.7	-	-	4.6	0.5	4.3	1.0	0.3	3.5
Placebo	1 <LLOQ	36.1	13.7	0.2	-	0.2	63.6	14.8	0.4	-	0.4	13.5	12.8	-	-	-
	2 LLOQ-UNR	1.9	33.4	2.1	-	0.2	2.1	9.7	-	-	-	1.7	52.8	3.8	-	0.3
	3 >UNR-2*UNR	-	0.8	2.5	-	0.2	-	-	-	-	-	-	1.4	4.5	-	0.3
	4 >2*UNR	-	-	0.6	0.2	-	-	-	-	-	-	-	-	1.0	0.3	-
	5 Missing	1.9	1.9	-	-	4.2	2.1	2.1	-	-	4.7	1.7	1.7	-	-	3.8
Active Comparator	1 <LLOQ	35.9	14.4	0.2	-	0.3	62.2	14.5	0.2	-	0.7	13.9	14.3	0.2	-	-
	2 LLOQ-UNR	1.3	34.7	2.3	-	0.1	1.6	10.6	1.4	-	-	1.0	54.9	3.1	-	0.2
	3 >UNR-2*UNR	-	0.3	1.3	0.3	-	-	-	0.7	-	-	-	0.6	1.7	0.6	-
	4 >2*UNR	-	0.1	0.4	1.2	-	-	-	-	0.2	-	-	0.2	0.8	1.9	-
	5 Missing	1.0	2.1	0.2	-	3.9	1.8	2.1	-	-	3.9	0.4	2.1	0.4	-	3.9

1¤: <LLOQ, 2¤: LLOQ-UNR [upper limit of the normal range], 3¤: >UNR-2*UNR, 4¤: >2*UNR, 5¤: Missing
Endpoint recorded at Wk 26 for Studies 1572, 1436, 1574 and 1697; and at Wk 28 for Study 1573
Source: Applicant's Table 215, pg 1531, Module 5.3.5.3, Appendix 7.2

From baseline to 26-28 weeks, there was a dose-dependent trend for liraglutide-treated women to shift from calcitonin values below the LLOQ to values within the range of quantitation. In the above table, the percentages of women who exhibited this upward shift were: AC = 14.5%; PBO = 14.8%; LGT 0.6 = 15.6%; LGT 1.2 = 16.8%, and LGT 1.8 = 19.2%. The percentage of women who exhibited this shift was numerically higher for each of the LGT dose groups than for either placebo or active comparator. This trend was not noted for men.

The table below sums the total percentage of patients who had an upward shift of any degree in calcitonin values from baseline to 26-28 weeks.

Table 7.1.3.3.2.4.2: Total Percentages of Patients Who had any Upward Shift in Calcitonin Levels From Baseline to 26-28 Weeks, LOCF, Five Major Phase 3 Trials

Treatment	Both Genders %	Women %	Men %
PBO	16.0	15.2	16.6
AC	17.2	16.1	18.2
LGT 0.6 mg	17.3	17.1	17.8
LGT 1.2 mg	16.2	17.2	15.1
LGT 1.8 mg	20.0	20.0	20.1

Source: Derived from Table 7.1.3.3.2.4.1 above

When examining the total percentage of patients who had an upward shift of any degree in calcitonin values from baseline to 26-28 weeks, the treatment group with the highest percentage

of upward shifters was the LGT 1.8 mg group for both genders. The 1.8 mg dose group had a numerically higher percentage of shifters than either of the other LGT doses, and a higher percentage than the placebo and active comparator groups. However, LGT dose-dependency was not noted for men.

The following two tables include information on shifts from baseline to 52 weeks, and from baseline to 76/78 weeks, respectively, for the two trials which had data beyond 28 weeks. These data should be interpreted with caution, because data beyond 26/28 weeks include some open-label extension periods, with the possibility for confounding. Also, the drop-out rate was high in extension studies, and was somewhat different between treatment groups (see Table 7.2.9.39.1).

Table 7.1.3.3.2.4.3: Percentages of Patients with Calcitonin Shifts, Baseline to Week 52 of Treatment, LOCF, Longterm Trials 1573 (Continued Main Trial) and 1572 (Continued into Open Label Extension), Data up to Time of NDA Submission

		Both sexes Endpoint After 52 weeks					Female Endpoint After 52 weeks					Male Endpoint After 52 weeks				
	Baseline	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤
Liraglutide 0.6mg	1 <LLOQ	41.8	6.0	-	-	-	81.1	2.7	-	-	-	15.5	8.2	-	-	-
	2 LLOQ-UNR	4.3	31.0	2.7	-	-	2.7	4.1	1.4	-	-	5.5	49.1	3.6	-	-
	3 >UNR-2*UNR	-	-	2.7	1.6	-	-	-	1.4	-	-	-	-	3.6	2.7	-
	4 >2*UNR	-	-	0.5	-	-	-	-	-	-	-	-	-	0.9	-	-
	5 Missing	4.9	3.8	0.5	-	-	6.8	-	-	-	-	3.6	6.4	0.9	-	-
Liraglutide 1.2mg	1 <LLOQ	34.7	10.0	-	-	0.2	58.1	9.3	-	-	0.5	11.2	10.7	-	-	-
	2 LLOQ-UNR	3.0	26.8	2.3	-	-	2.8	7.4	0.5	-	-	3.3	46.3	4.2	-	-
	3 >UNR-2*UNR	-	0.7	1.9	-	-	-	0.5	0.5	-	-	-	0.9	3.3	-	-
	4 >2*UNR	-	-	0.2	0.5	-	-	-	-	0.5	-	-	-	0.5	0.5	-
	5 Missing	2.8	1.2	-	-	15.6	5.1	-	-	-	14.9	0.5	2.3	-	-	16.4
Liraglutide 1.8mg	1 <LLOQ	31.4	10.0	0.2	-	-	57.7	9.3	0.5	-	-	8.8	10.6	-	-	-
	2 LLOQ-UNR	3.8	27.6	1.9	-	-	1.5	7.2	1.5	-	-	5.8	45.1	2.2	-	-
	3 >UNR-2*UNR	-	0.2	1.0	1.4	-	-	-	0.5	-	-	-	0.4	1.3	2.7	-
	4 >2*UNR	-	-	0.5	-	-	-	-	-	-	-	-	-	0.9	-	-
	5 Missing	4.3	2.4	0.5	0.5	14.3	5.7	1.0	-	-	14.9	3.1	3.5	0.9	0.9	13.7
Placebo	1 <LLOQ	39.3	11.5	-	-	-	66.7	12.5	-	-	-	21.6	10.8	-	-	-
	2 LLOQ-UNR	6.6	31.1	1.6	-	-	4.2	-	-	-	-	8.1	51.4	2.7	-	-
	3 >UNR-2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	4 >2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5 Missing	8.2	1.6	-	-	-	16.7	-	-	-	-	2.7	2.7	-	-	-
Active Comparator	1 <LLOQ	31.6	11.8	-	-	0.2	54.1	9.3	-	-	0.5	13.1	13.9	-	-	-
	2 LLOQ-UNR	4.2	26.9	2.1	-	-	4.1	6.2	1.5	-	-	4.2	43.9	2.5	-	-
	3 >UNR-2*UNR	-	0.5	0.5	0.2	-	-	-	-	-	-	-	0.8	0.8	0.4	-
	4 >2*UNR	-	0.2	-	0.9	-	-	-	-	-	-	-	0.4	-	1.7	-
	5 Missing	0.9	2.1	-	-	17.9	1.0	1.5	-	-	21.6	0.8	2.5	-	-	14.8

1¤: <LLOQ, 2¤: LLOQ-UNR, 3¤: >UNR-2*UNR, 4¤: >2*UNR, 5¤: Missing
Source: Applicant's Table 216, pg 1532, Module 5.3.5.3, Appendix 7.2

Table 7.1.3.3.2.4.4: Percentages of Patients with Calcitonin Shifts, Baseline to Weeks 76-78 of Treatment, LOCF, Longterm Trials 1572 and 1573 (Both Trials Continued into Open Label Extension), Data up to Time of NDA Submission

		Both sexes Endpoint After 76/78 weeks					Female Endpoint After 76/78 weeks					Male Endpoint After 76/78 weeks				
	Baseline	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤
Liraglutide 0.6mg	1 <LLOQ	44.0	2.2	-	-	-	81.1	-	-	-	-	19.1	3.6	-	-	-
	2 LLOQ-UNR	14.1	20.1	1.1	-	-	6.8	-	-	-	-	19.1	33.6	1.8	-	-
	3 >UNR-2*UNR	-	0.5	2.2	1.6	-	-	1.4	-	-	-	-	-	3.6	2.7	-
	4 >2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5 Missing	4.3	2.7	-	-	7.1	5.4	-	-	-	5.4	3.6	4.5	-	-	8.2
Liraglutide 1.2mg	1 <LLOQ	43.1	6.4	-	-	-	67.9	6.7	-	-	-	17.9	6.2	-	-	-
	2 LLOQ-UNR	10.4	23.9	2.1	0.3	-	3.6	8.5	-	-	-	17.3	39.5	4.3	0.6	-
	3 >UNR-2*UNR	0.3	1.2	1.2	0.3	-	0.6	-	-	-	-	-	2.5	2.5	0.6	-
	4 >2*UNR	-	-	0.3	0.6	-	-	-	-	0.6	-	-	-	0.6	0.6	-
	5 Missing	4.0	0.6	-	-	5.2	6.1	-	-	-	6.1	1.9	1.2	-	-	4.3
Liraglutide 1.8mg	1 <LLOQ	36.6	7.0	-	-	-	63.5	6.1	-	-	-	14.4	7.8	-	-	-
	2 LLOQ-UNR	13.1	22.0	2.4	-	-	5.4	6.8	0.7	-	-	19.4	34.4	3.9	-	-
	3 >UNR-2*UNR	-	0.9	1.5	0.3	-	-	-	0.7	-	-	-	1.7	2.2	0.6	-
	4 >2*UNR	-	-	0.3	0.3	-	-	-	-	-	-	-	-	0.6	0.6	-
	5 Missing	6.1	1.8	0.3	0.3	7.0	8.1	0.7	-	-	8.1	4.4	2.8	0.6	0.6	6.1
Placebo	1 <LLOQ	37.7	3.3	-	-	-	66.7	4.2	-	-	-	18.9	2.7	-	-	-
	2 LLOQ-UNR	19.7	8.2	1.6	-	-	-	4.2	-	-	-	32.4	10.8	2.7	-	-
	3 >UNR-2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	4 >2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5 Missing	8.2	-	-	-	21.3	16.7	-	-	-	8.3	2.7	-	-	-	29.7
Active Comparator	1 <LLOQ	39.1	8.8	-	0.3	-	64.7	9.0	-	0.8	-	20.9	8.6	-	-	-
	2 LLOQ-UNR	12.2	22.2	2.8	-	-	5.3	8.3	0.8	-	-	17.1	32.1	4.3	-	-
	3 >UNR-2*UNR	-	0.6	0.9	-	-	-	-	-	-	-	-	1.1	1.6	-	-
	4 >2*UNR	-	0.3	-	0.9	-	-	-	-	-	-	-	0.5	-	1.6	-
	5 Missing	2.5	1.6	-	-	7.8	3.8	-	-	-	7.5	1.6	2.7	-	-	8.0

1¤: <LLOQ, 2¤: LLOQ-UNR, 3¤: >UNR-2*UNR, 4¤: >2*UNR, 5¤: Missing
Endpoint recorded at Wk 76 for Study 1573 and Wk 78 for Study 1572
Source: Applicant's Table 217, pg 1533, Module 5.3.5.3, Appendix 7.2

As mentioned earlier, data from the above two tables should be interpreted with caution, because they include some open-label extension data from voluntary unblinded extensions. The percentage of missing data is higher for these time periods than for the period from baseline to 26/28 weeks. Both these factors may result in confounding. Clear patterns of upward shifts which distinguish liraglutide from comparators are not identified. It appears that overall, a lower percentage of patients at these points still had a calcitonin value which remained above their baseline, indicating that some patients who had shifted above normal earlier in the trial might later have returned to baseline, but the confounding factors prevent assurance in this observation.

The applicant performed a repeated measurement analysis on data from Weeks 12 and 26/28 from the five major Phase 3 trials. These analyses are presented in the following table. The clinical safety reviewer views the p-values from this statistical analysis model as exploratory findings, because this analysis is part of a larger exploratory evaluation of many safety endpoints. The statistical estimates and p-values from this analysis model may be useful in identifying possible trends and relationships for further study. Also of note is the fact that the pooled safety database combines data from studies that are each designed somewhat differently, with respect to the study arms and to the patient population. For this reason, relationships identified from this statistical analysis model should be viewed as exploratory findings.

Table 7.1.3.3.2.4.5: Repeated Measurement Analyses for Calcitonin, Five Major Phase 3 Trials

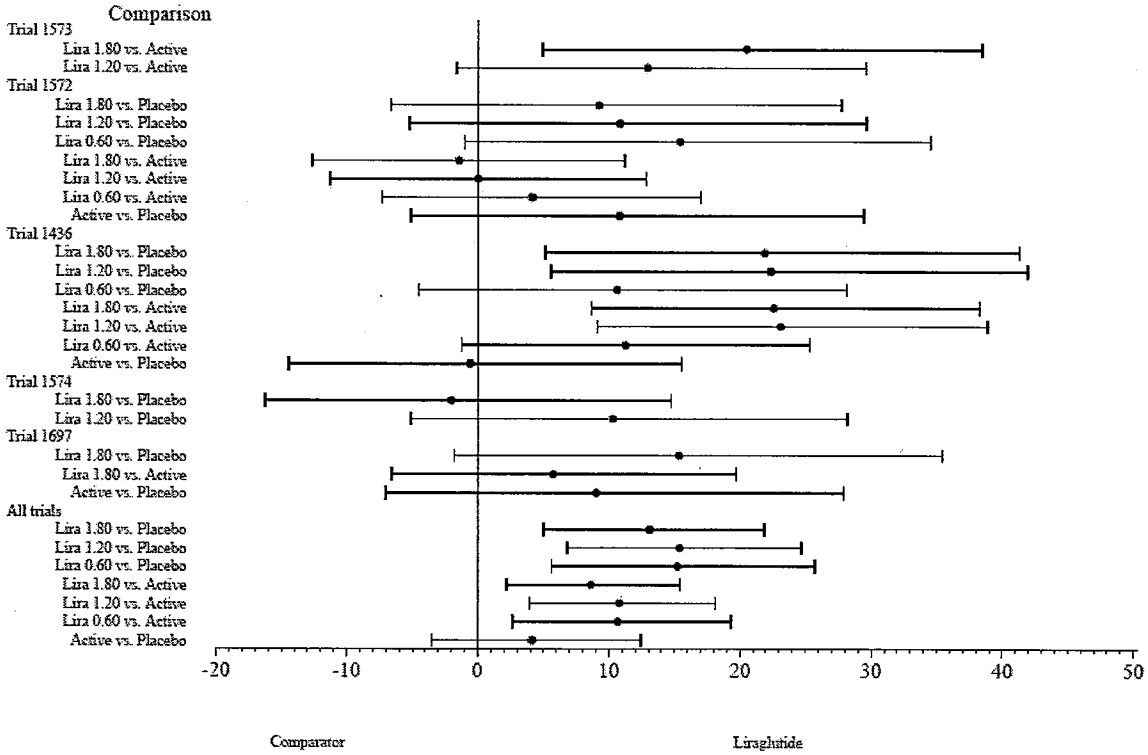
Week	Treatment	Calcitonin (ng/L) LS Mean (95% CI)	Comparison	Relative Difference % (95% CI)	p-value
12	LGT 1.8 mg	0.76 (0.72, 0.81)			
	LGT 1.2 mg	0.78 (0.73, 0.83)			
	LGT 0.6 mg	0.78 (0.72, 0.84)			
	AC	0.70 (0.66, 0.74)			
	PBO	0.67 (0.63, 0.73)			
			LGT 1.8 vs. PBO	13.0 (4.8, 21.8)	0.0014
			LGT 1.2 vs. PBO	15.4 (6.7, 24.7)	0.0003
			LGT 0.6 vs. PBO	15.2 (5.5, 25.7)	0.0015
			LGT 1.8 vs. AC	8.6 (2.2, 15.4)	0.0080
			LGT 1.2 vs. AC	10.9 (3.9, 18.3)	0.0017
			LGT 0.6 vs. AC	10.7 (2.6, 19.4)	0.0084
			AC vs. PBO	4.0 (-3.7, 12.4)	0.3118
26	LGT 1.8	1.01 (0.95, 1.06)			
	LGT 1.2	0.99 (0.94, 1.05)			
	LGT 0.6	0.96 (0.90, 1.04)			
	AC	0.97 (0.91, 1.02)			
	PBO	0.89 (0.83, 0.95)			
			LGT 1.8 vs. PBO	13.6 (6.1, 21.6)	0.0003
			LGT 1.2 vs. PBO	11.8 (4.1, 20.2)	0.0023
			LGT 0.6 vs. PBO	8.8 (0.3, 17.9)	0.0428
			LGT 1.8 vs. AC	4.3 (-1.6, 10.4)	0.1542
			LGT 1.2 vs. AC	2.7 (-3.5, 9.2)	0.4024
			LGT 0.6 vs. AC	-0.1 (-7.1, 7.3)	0.9683
			AC vs. PBO	8.9 (1.5, 16.9)	0.0181

Source: Applicant's Table 3-4, Module 2.7.4, pg 185
For description of analysis methods, see pages 183-184 of Module 2.7.4. Repeated measurement analysis for normal censored data. Logarithm of calcitonin was censored response. Trial time, treatment, gender and treatment by time interaction were fixed effects. Subjects entered as random effects. Calcitonin values at LLOQ (0.7 ng/L) were considered censored results; incorporated into statistical model by adding the information into the likelihood function. The contribution to the likelihood function for the censored terms corresponds to the distribution function taken at 0.7 ng/L.

At Week 12, mean calcitonin levels were higher for all three LGT dose groups than for either PBO or active comparator. Relative percent differences were statistically significant for comparisons of all LGT doses versus either PBO or active comparator. At Week 26, relative percent differences remained statistically significantly different for comparisons of LGT to PBO, but not for LGT versus active control. Of note from this table is the fact that the lower limit of quantitation for the assay was 0.7 ng/L, and mean values at these time points do not fall much above the LLOQ. Most patients at baseline had values that fell below the lower limit of quantitation, and therefore the applicant's analyses may have been influenced by how their model handled values that were below the LLOQ. The Agency considers these analyses to be exploratory.

The following two forest plots display relative differences between treatment arms in each of the five major Phase 3 trials at 12 and 26 weeks.

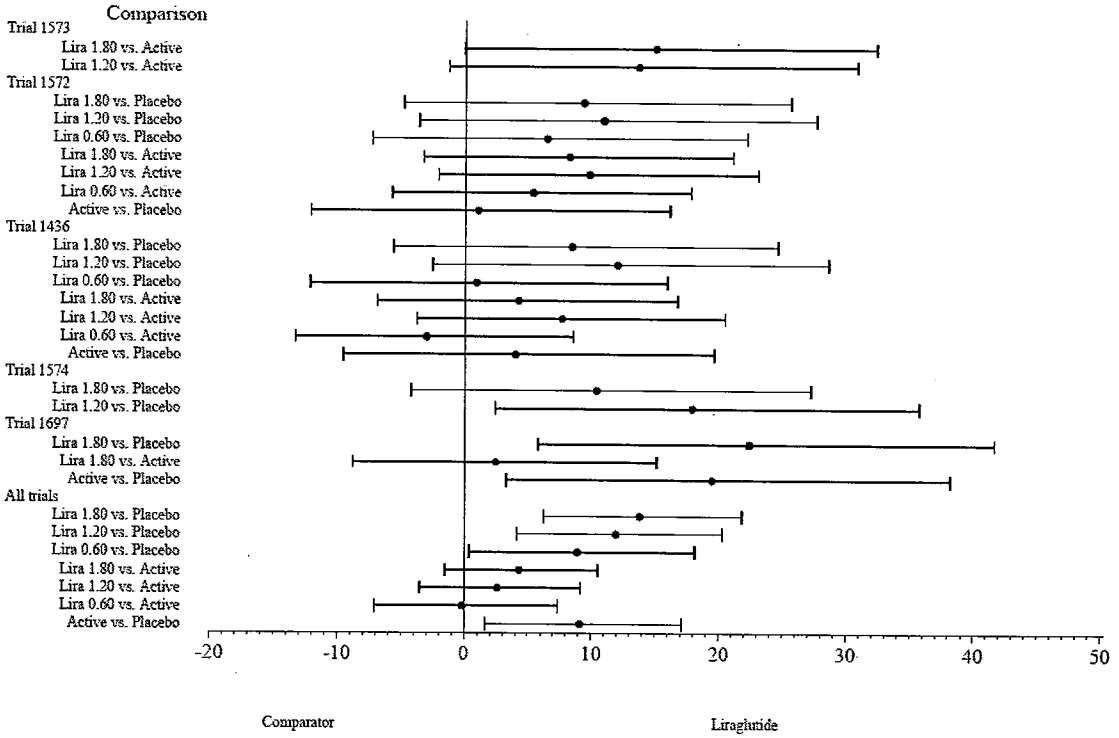
Figure 7.1.3.3.2.4.3: Forest Plot of Calcitonin Continuous Analysis (Percent Relative Difference), Five Major Phase 3 Trials, Week 12



Source: Applicant's Figure 83, Module 5.3.5.3, pg 2982

At Week 12, for the combined data, all relative differences between liraglutide and comparator are statistically significantly different. In individual trials, the point estimate for the relative difference for most treatment comparisons is consistent with higher calcitonin values for liraglutide than comparator, although many of these confidence intervals include zero. Liraglutide dose dependency for calcitonin relative differences is not demonstrated.

Figure 7.1.3.3.2.4.4: Forest Plot of Calcitonin Continuous Analysis (Percent Relative Difference), Five Major Phase 3 Trials, Week 26/28



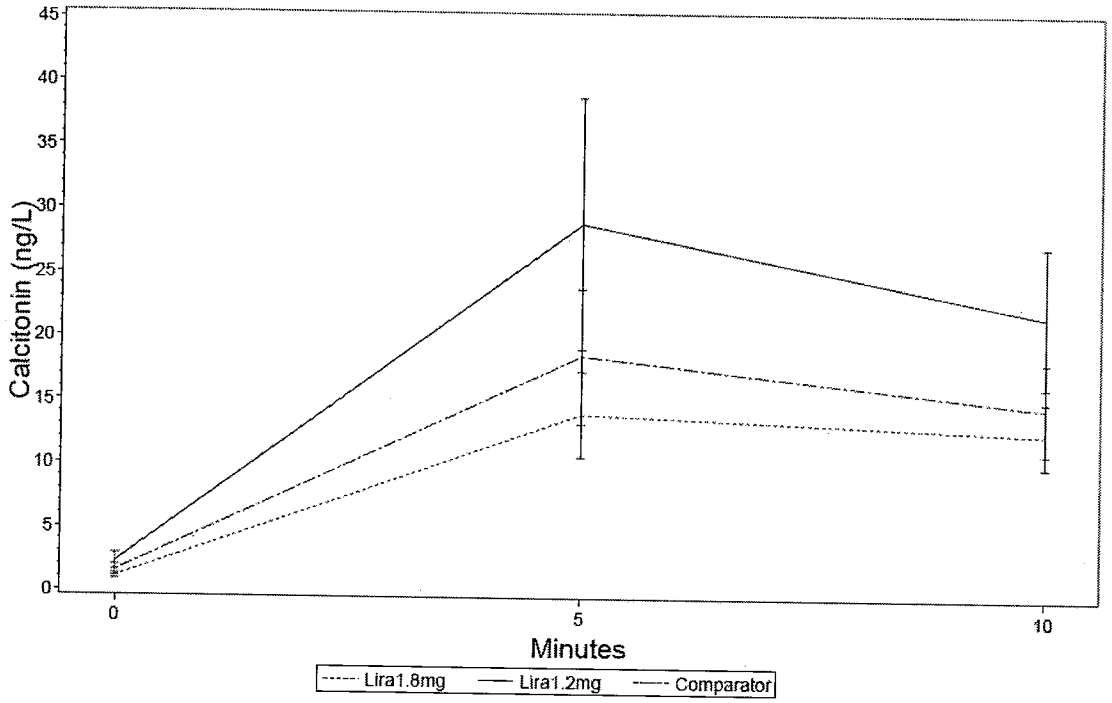
Source: Applicant's Figure 3-9, Module 2.7.4, pg 192

At 26/28 weeks, fewer relative differences are statistically significantly different for liraglutide versus comparator. Point estimates for almost all treatment comparisons are consistent with higher calcitonin values for liraglutide than for comparator, although many of these confidence intervals include zero. In the combined trials, there appears to be a pattern of liraglutide dose-dependence for increasing calcitonin relative differences. Overall, relative differences are higher for liraglutide versus placebo than for liraglutide versus active comparator.

Calcium stimulation tests were performed on a subset of patients (total N=144) from Study 1573 (Weeks 0 and 52; 90 patients included) and Study 1574 (Weeks 0 and 26; 54 patients included). Calcium or pentagastrin stimulation tests were used in the past (prior to the availability of RET proto-oncogene testing) in the evaluation of family members of patients with known medullary thyroid carcinoma, in an effort to identify MTC in family members at an early stage. Use of the stimulation test was based on the observation that basal calcitonin levels were sometimes not elevated in patients with C-cell hyperplasia or small tumors, but often increased to abnormally high levels after stimulation with calcium and/or pentagastrin (Becker 1995). Calcium stimulation tests are not used as commonly now. The usefulness of this test in the setting of evaluation of a potential drug-induced C-cell disorder is unknown. In this test, fasting subjects received 2 mg elemental calcium (as calcium gluconate) per kg of body weight, infused intravenously over 5 minutes. Blood samples were obtained at times 0, 5 and 10 minutes.

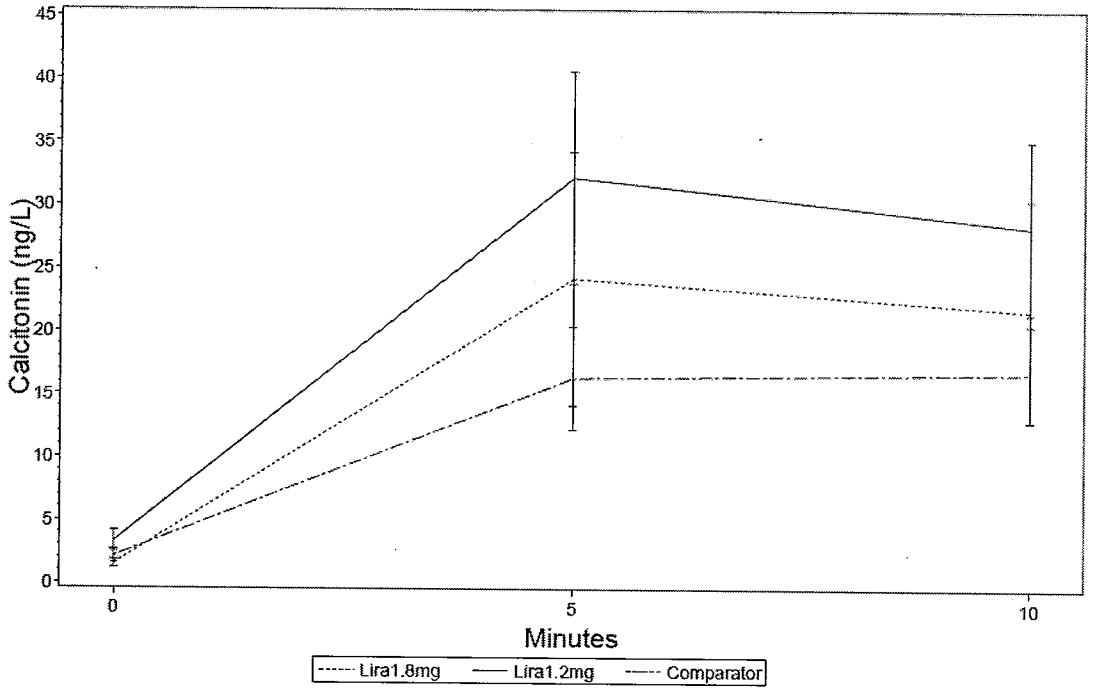
Treatments included LGT 1.8 mg, LGT 1.2 mg, and comparator. Study 1573 used an active comparator (glimepiride), and Study 1574 used an add-on placebo-controlled design, in which either LGT or PBO was added to baseline combination metformin and rosiglitazone. At end of trial (26 or 52 weeks, LOCF), stimulated calcitonin values were highest in the 1.2 mg LGT group, intermediate in the 1.8 mg LGT group, and lowest in comparator. There was no statistically significant difference between LGT and comparator, as illustrated in the following graphs. However, mean peak stimulated calcitonin levels were higher at end-of-study than at baseline in the LGT groups.

Figure 7.1.3.3.2.4.5: Mean Calcitonin Values (ng/L) During Calcium Stimulation Test, Week Zero, Studies 1573 and 1574



Source: Applicant's Figure 124, pg 3023, Module 5.3.5.3

Figure 7.1.3.3.2.4.6: Mean Calcitonin Values (ng/L) During Calcium Stimulation Test, End-of-Study (LOCF), Studies 1573 and 1574



Source: Applicant's Figure 125, pg 3024, Module 5.3.5.3

On 8 Jul 2009, the applicant submitted corrected calcitonin data for preliminary analyses of 2-year extension data, and other analyses using data that were not available at the time of submission of the NDA. Corrected analyses had been required because of prior programming errors by the applicant. All calcitonin values and analyses presented in this review are from data that were either not affected by the programming error, or from corrected data. Please see Section 7.2.9.39 for further discussion of these data. In summary:

- Mean calcitonin levels over two years remained near the lower limit of quantitation, and were not different between treatment groups. Drop-out rates were high, and were somewhat different between treatment groups.
- Patients who had elevated calcitonin at baseline did not tend to have further increases in calcitonin over time.
- In repeated measures analyses similar to those performed for the original NDA, mean differences were statistically significant for all doses of liraglutide versus MET, and for all doses of liraglutide versus total comparator, at 12 weeks. At 26 weeks, mean differences did not favor liraglutide in any group, but were statistically significant only for the 1.8 mg and 1.2 mg doses versus MET, and for the 1.8 mg dose versus total comparator. Mean differences were small in absolute terms.

In general, the mean calcitonin changes in the liraglutide development program were small. Most human medullary thyroid cancers are associated with calcitonin values >50 ng/L, although as mentioned earlier, calcitonin may not have been a reliable biomarker for the C-cell tumor

findings in animal studies of liraglutide. In general, however, it was historically a useful biomarker for the naturally-occurring forms of human medullary thyroid carcinoma.

After a request from the Division, the applicant submitted summary data regarding percentages of patients who developed calcitonin values ≥20 and ≥50 ng/L. The following table summarizes these data, which were submitted on 25 Jun 2009.

Table 7.1.3.3.2.4.6: Percentages of Patients Who Developed Serum Calcitonin Values ≥20 and ≥50 ng/L, All Phase 3 Trials of Liraglutide as of 24 Jun 2009, Including Main Trial and Extension Data

Treatment	BL Calcitonin <20 and any Post-BL Calcitonin ≥20 ng/L n (%)	BL Calcitonin <50 and any Post-BL Calcitonin ≥50 ng/L n (%)
LGT 0.6	3 (0.53)	
LGT 1.2	6 (0.67)	
LGT 1.8	19 (1.39)	2 (0.15)
Pooled LGT	28 (0.88)	2 (0.06)
Pooled Comp	11 (0.57)	1 (0.05)
PBO	1 (0.16)	
AC	10 (0.76)	1 (0.08)

Source: Applicant's Table 2, pg 14, submission stamp date 25 Jun 2009 (1 of 3 submissions that day to NDA 22341)

There were few cases of new elevations of calcitonin to ≥50 ng/L, and there was no difference in the incidence between liraglutide and comparator. The incidence of new elevations of calcitonin to ≥20 ng/L was numerically higher for liraglutide (0.88%) than for comparator (0.57%), and there appeared to be a dose-related trend. However, when looking at comparator groups separately, only the 1.8 mg LGT dose group (1.39%) had an incidence higher than the active comparator group (0.76%).

While calcitonin has been the most commonly used biomarker for medullary thyroid carcinoma, there are other possible biomarkers. These were not routinely measured in the liraglutide development program, but could possibly be used in future trials as supportive assessments of evidence of C-cell activation.

Carcinoembryonic antigen (CEA) is routinely used in the follow-up of patients with known medullary thyroid carcinoma. It is somewhat less sensitive than calcitonin (Franke 2000), but is sometimes positive in patients whose medullary thyroid cancers do not produce calcitonin (Giovanella 2008). Other cancers, particularly colon cancer, may also be associated with elevated CEA. There have been case reports of elevated CEA preceding an overt diagnosis of MTC by years (Fallahi 1998) in patients who did not have other causes of elevated CEA. Carcinoembryonic antigen correlates with extent of disease in MTC, and can be used to differentiate between stable and progressive MTC (de Groot 2006, Machens 2007). It correlates strongly with disease progression (Laure Giraudet 2008) and aggressivity/dedifferentiation (Mendelsohn 1984). High CEA levels are predictive of poor likelihood of surgical cure (Machens 2007). Assays for CEA are readily commercially available.

Procalcitonin, the precursor peptide to mature calcitonin, is present in the majority of patients with medullary thyroid carcinoma (Bihan 2003, Bolko 2003). Its levels in MTC considerably exceed those of mature calcitonin, perhaps making it easier to detect. Procalcitonin is also a more analytically stable peptide than calcitonin, which undergoes rapid *in vitro* degradation after collection and is very dependent on appropriate handling of samples for accuracy of results (Algeciras-Schimnich 2009). Currently, procalcitonin is used as an early marker of sepsis, and commercial assays are available.

Chromogranin A has also been shown to be elevated in medullary thyroid carcinoma, and levels correlate with tumor mass and number of metastases (Franke 2000). However, it appears to have less sensitivity and specificity when used for MTC screening than it does for screening for certain other neuroendocrine-derived tumors (Baudin 2001, Franke 2000, Seregni 2001).

Medullary thyroid carcinomas may produce a number of substances, including catecholamines, serotonin and histamine metabolites. Studies have been conducted of the use of plasma catecholamines; platelet serotonin; tryptase; and urinary markers of catecholamine, histamine and serotonin metabolism, but these markers have thusfar not been clinically useful in detection of MTC (de Groot 2006).

It appears that procalcitonin and CEA could be used in clinical trials of liraglutide to complement calcitonin measurements, and that these tests could provide additional possible assessments of C-cell activation.

7.1.3.3.2.5. Nonmalignant Thyroid Adverse Events

The following table summarizes nonmalignant serious thyroid-related adverse events.

Table 7.1.3.3.2.5.1: Nonmalignant Thyroid-related Serious Adverse Events

Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
	n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
Benign neoplasm of thyroid gland	1	<0.1	0.4	0	0	0
Goitre	3	0.1	1.3	0	0	0
Thyroid disorder	1	<0.1	0.4	0	0	0

Source: Applicant's Table 72, beg pg 1123 ISS

Patient 222002 had events of goitre and elevated blood calcitonin. This was a 56 year old German man who presented after 206 days of LGT at 1.8 mg/day with "struma nodosa". He also had an elevated calcitonin level of 7.05 pmol/L (normal range 0.2-2.46). His serum calcitonin continued to increase; 3 months later it was reported at 23.4 pg/mL (nl range <18.9). An ultrasound revealed a right thyroid nodule; scintigraphy was consistent with "struma nodosa". Medullary thyroid cancer was suspected. Six weeks after the ultrasound, the thyroid nodule was excised and was benign. He recovered from surgery uneventfully. Regular sonography and calcitonin levels were planned for follow-up.

Patient 232004 had events of goitre and elevated blood calcitonin. This was a 47 year old German woman who presented with elevated blood calcitonin (level not mentioned) and a solitary right thyroid nodule after 27 days of run-in metformin therapy. Although she was randomized to liraglutide, the narrative states she never received the drug. Eight months after the elevated calcitonin and the nodule were noted, she underwent resection of the nodule, which was benign. One month postoperatively, her calcitonin level was reported as normal.

Patient 261006 had events of benign neoplasm of thyroid gland, thyroid disorder, and papillary thyroid cancer. This patient is further discussed in Section 7.1.3.3.2.2.1.

Patient 326016 had events of goitre and papillary thyroid cancer. This patient is further discussed in Section 7.1.3.3.2.2.1.

There are too few cases of nonmalignant serious thyroid disorders to assign causality to liraglutide.

Across all trials of liraglutide at the time of NDA submission, thyroid adverse events occurred with higher numerical frequency among LGT-treated patients than among comparator-treated patients, as shown in the following table:

Table 7.1.3.3.2.5.2: Overall Summary of Incidence of Thyroid Events, All Completed Trials at Time of NDA Submission

	LGT N=4211 PY=2241	Non-LGT N=2272 PY=1139
Number of subjects with serious thyroid adverse events (%)	7 (0.2)	1 (<0.1)
Number of serious thyroid adverse events	10	1
Total number of subjects with thyroid adverse events (serious + nonserious)	61 (1.4)	24 (1.1)
Total number of thyroid adverse events (serious + nonserious)	80	25
Number of serious thyroid adverse events per 1000 PY	4.5	0.9
Number of overall thyroid adverse events per 1000 PY (serious + nonserious)	35.7	22.0

Source: Applicant's Table 2-16, pg 107, ISS
Abbreviations: LGT = liraglutide, PY = patient-years

Thyroid adverse events also occurred at a higher numerical rate per unit of patient-time among LGT-exposed patients than among comparator patients.

In the four trials which were ongoing at the time of submission of the NDA, there was a similar imbalance of thyroid adverse events; some data were still blinded.

Table 7.1.3.3.2.5.3: Summary of Incidence of Thyroid Events, Ongoing Trials at Time of NDA Submission

	LGT N=714 PY=602	Non-LGT N=362 PY=294	Blinded N=467 PY=164
Number of subjects with serious thyroid adverse events (%)	1 (0.1)	0	1 (0.2)
Number of serious thyroid adverse events	1	0	1
Total number of subjects with thyroid adverse events (serious + nonserious) (%)	10 (1.4)	2 (0.6)	5 (1.1)
Total number of thyroid adverse events (serious + nonserious)	10	2	6
Number of serious thyroid adverse events per 1000 PY	1.7	0	6.1
Number of overall thyroid adverse events per 1000 PY (serious + nonserious)	16.6	6.8	36.5

Source: Applicant's Table 2-17, pg 108, ISS

The applicant reports that, although patient-time data were still blinded in the ongoing trials, it was known that three of the events occurred among patients treated with LGT 1.8 mg and two occurred among patients treated with exenatide. For LGT, one patient had an event of autoimmune thyroiditis and thyroid neoplasm (Patient 476001) and two patients had increased calcitonin (Patients 352004 and 352013). The thyroid events among exenatide-treated patients in the blinded studies were both events of hyperthyroidism (Patients 206005 and 207002).

Dose dependency was not noted for thyroid events in completed trials, as shown in the following table:

Table 7.1.3.3.2.5.4: Rates of Thyroid Adverse Events by LGT Dose, Completed Trials at Time of NDA Submission

	<0.6 mg	0.6 mg	>0.6 and <1.2 mg	1.2 mg	>1.2 and <1.8 mg	1.8 mg	>1.8 mg
Number of patients	377	641	417	993	73	1408	302
Number of patient-years	64	418	39	758	12	870	82
Number of serious thyroid adverse events per 1000 PY	0	4.8	0	5.3	0	4.6	0
Total number of thyroid adverse events per 1000 PY (serious + nonserious)	141.6	38.3	76.9	33.0	0	29.9	12.2

Source: Applicant's Table 2-18, pg 108, ISS

The following table presents adverse thyroid events by System Organ Class and Preferred Term.

Table 7.1.3.3.2.5.5: Thyroid Adverse Events, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate per 1000 PY	n	%	Rate per 1000 PY
Any	Any thyroid term	61	1.4	35.7	24	1.1	22.0
Investigations	Any thyroid term	30	0.7	14.3	13	0.6	11.4
	Blood calcitonin increased	25	0.6	11.6	10	0.4	8.8
	Blood TSH increased	3	0.1	1.8	2	0.1	1.8
	Blood calcitonin abnormal	1	<0.1	0.4	0	0	0
	Thyroxine decreased	1	<0.1	0.4	0	0	0
	Blood TSH decreased	0	0	0	1	<0.1	0.9
Endocrine disorders	Any thyroid term	21	0.5	11.6	7	0.3	6.1
	Goitre	15	0.4	7.1	1	<0.1	0.9
	Hypothyroidism	3	0.1	1.3	4	0.2	3.5
	Hyperthyroidism	2	<0.1	0.9	0	0	0
	Thyroid cyst	2	<0.1	0.9	0	0	0
	Thyroid disorder	2	<0.1	0.9	0	0	0
	Autoimmune thyroiditis	1	<0.1	0.4	2	0.1	1.8
Neoplasms	Any thyroid term	19	0.5	9.8	5	0.2	4.4
	Thyroid neoplasm	15	0.4	7.1	4	0.2	3.5
	Papillary thyroid cancer	4	0.1	1.8	1	<0.1	0.9
	Benign neoplasm of thyroid gland	1	<0.1	0.4	0	0	0
	Parathyroid tumor benign	1	<0.1	0.4	0	0	0

Source: Applicant's Table 2-19, pg 110, ISS
Abbreviations: LGT = liraglutide, PY = patient-years, TSH = thyroid stimulating hormone

Events which occurred with a higher numerical frequency among LGT-treated patients than among comparator-treated patients included blood calcitonin increased, goitre, and thyroid neoplasm. One of the events listed under the Preferred Term "thyroid disorder" was a case of diffuse C-cell hyperplasia (Patient 261006).

Regarding the term thyroid neoplasm, 14/19 events (3 PBO, 11 LGT) came from a single study (1334), which was performed in Japan. This study was one of four studies in which thyroid ultrasounds were performed, and in this study, the appearance of thyroid nodules on ultrasound was reported as an adverse event for some, but not all, patients who were found to have a nodule on ultrasound. See Table 7.1.3.3.2.5.6 below.

The Preferred Term "goitre" was applied to a variety of verbatim descriptions of thyroid events, including "struma nodosa" (n=4), and one case each of "goitre nodular", "la goitre", "increase size thyroid left lobe", "increasing awareness of existing goitre", "multinodular goitre", "nodular goitre", "nontoxic struma unidosa right side", "struma unidosa nontoxic", "swollen thyroid right lobe", "thyroid enlargement", "thyromegaly", "thyromegaly left lobe with cystic mass" and "worsening of thyroid goitre".

As mentioned earlier in the discussion of cardiovascular events, the terms "flushing" and "hot flush" were reported slightly numerically more frequently for liraglutide-treated patients than for comparator-treated patients. Each of these terms was reported for only 1 comparator-treated patient (<0.1%). "Flushing" was reported for 9 (0.2%) of liraglutide-treated patients, and "hot flush" was reported for 7 (0.2%) of liraglutide-treated patients. Medullary thyroid carcinoma is a rare entity in the differential diagnosis of flushing, although other causes of flushing are much more common.

Thyroid ultrasound was performed at baseline and end-of-study in four trials (1334, 1571, 1636 and 1694). In these trials, no patient had appearance of a new nodule ≥10 mm in diameter, and no patient had growth of an existing nodule by ≥10 mm. However, the longest duration of these trials was 14 weeks, which is a short observation time for the assessment of stimulation of thyroid nodule growth. In examining the study results for Study 1334, which was a 14-week study performed in Japan, new appearance of smaller thyroid nodules (<10 mm) was common, but did not appear to occur with significantly higher frequency among liraglutide-treated patients than among placebo-treated patients.

Table 7.1.3.3.2.5.6: Incidence of New Thyroid Nodules <10 mm in Diameter, Week 14, Study 1334 (LOCF)

Treatment Group	N	# New Thyroid Nodules	% With New Thyroid Nodule
PBO	44	4	9.1
LGT 0.1 mg	45	6	13.3
LGT 0.3 mg	46	1	2.2
LGT 0.6 mg	45	5	11.1
LGT 0.9 mg	44	5	11.4
Any LGT	180	17	9.4

Source: Module 5, Clinical Trial Report for 1334, Table 12-13, pg 117

7.1.3.3.2.6. Summary of Observations Regarding Thyroid Cancer and Calcitonin

The following bullets summarize observations regarding C-cell tumors, C-cell hyperplasia, and calcitonin.

- Carcinogenicity studies in rats and mice have demonstrated an increased incidence of thyroid C-cell tumors associated with liraglutide administration in these species. These tumors occurred in both species, in both genders, at clinically relevant exposures. The Pharmacology/Toxicology reviewer considers this to be a strong animal signal.
- A similar signal is being noted in interim carcinogenicity data for some other long-acting (q day or longer) GLP-1 analogues in development.
- The applicant's mechanistic studies did not definitely demonstrate that these rodent findings are not relevant to humans.
- The applicability of these rat and mouse findings to humans is not fully understood. Calcitonin physiology may differ between rodents and humans.
- In the animal studies of liraglutide, calcitonin may not have been a reliable biomarker for risk of development of these C-cell tumors.

- No drug that has caused C-cell tumors in two species is known to have been approved by the FDA for use in humans. It is not known if such a drug has ever been submitted for consideration for approval before.
- There have not been cases of medullary thyroid carcinoma in humans who received liraglutide, but one might not expect to see this relatively indolent tumor over the duration of a typical drug development program, even if the drug carried a true increased risk for MTC.
- There has been one case of "medullary carcinoma *in situ*" for a liraglutide-treated patient, and one case for a comparator-treated patient. There is an additional recently-reported case of focal C-cell hyperplasia in a liraglutide-treated patient, and 3 additional cases of diffuse C-cell hyperplasia in liraglutide-treated patients. There were no other cases of CCH in comparator-treated patients. This total of 5 versus 1 cases of CCH for LGT versus comparator represents approximate rates per 1000 patient-years of 1.7 (5 cases/2882 PY) and 0.7 (1 case/1486 PY), respectively.
- It is difficult to know whether the literature regarding the pathologic features of human C-cell hyperplasia is fully relevant to a possible drug-induced condition, because most of the literature is derived from studies of kindreds with familial medullary thyroid carcinoma.
- Liraglutide did not demonstrate a marked effect on calcitonin values. Mean values remained near the lower limit of quantitation over time in blinded controlled trials out to 26 weeks, and in voluntary unblinded extensions as far out as two years. However, dropout rates were high in these extensions, and were somewhat different between treatment groups.
- Patients who began with elevated calcitonin did not tend to have further increases over time.
- Among patients who began study with calcitonin values <50 ng/L, two liraglutide-treated patients and one comparator-treated patient developed calcitonin levels >50 ng/L (ratio 1:1).
- Although liraglutide did not exhibit marked effects on calcitonin, it may have had some lesser effects.
- In the five major Phase 3 clinical trials of liraglutide, there was a dose-dependent trend for liraglutide-treated women (but not for men) to shift from calcitonin values below the lower limit of quantitation to within the range of quantitation, from baseline to 26 or 28 weeks of treatment.
- In the five major Phase 3 trials, when examining the total percentage of patients (men or women) who had an upward shift of any degree in calcitonin values from baseline to 26 or 28 weeks of treatment, the treatment group with the highest percentage of upward shifters was the liraglutide 1.8 mg dose group. The 1.8 mg dose group had a numerically higher percentage of shifters than either of the other liraglutide doses (1.2 or 0.6 mg), and a higher percentage than the placebo and active comparator groups. However, liraglutide dose-dependency was not noted in this observation.
- In the five major Phase 3 trials, repeated measurement analyses showed that at Week 12, mean calcitonin levels were statistically significantly higher for all doses of liraglutide versus placebo, and for all doses of liraglutide versus active control. At Week 26, differences remained significant for liraglutide versus placebo, but not for liraglutide versus active control. These analyses should be considered exploratory in nature.
- When examining a forest plot of calcitonin data from all five major Phase 3 trials, in the combined trials, there appears to be a pattern of liraglutide dose-dependence at Week 26/28 but not at Week 12. That is, the point estimates for liraglutide versus comparator at Week 26/28 are successively higher for the 0.6, 1.2 and 1.8 mg liraglutide doses. Relative

differences are greater for liraglutide versus placebo than for liraglutide versus active comparator, but the pattern of liraglutide dose-dependence occurs for both comparators.

- The incidence of new elevations of calcitonin to >20 ng/L was numerically higher for liraglutide (0.88%) than for comparator (0.57%), and there appeared to be a dose-related trend. The highest percentage of patients who developed a new elevation of calcitonin to >20 ng/L was among patients in the liraglutide 1.8 mg group (1.39%).
- The clinical significance of small changes in calcitonin in this setting is uncertain.

Overall, there is a strong animal signal for thyroid C-cell tumors, and human relevance has not been excluded. Human clinical trials have not been of sufficient duration to provide adequate controlled, blinded data to fully assess the human risk.

If liraglutide is approved, questions will arise regarding the need for baseline screening for medullary thyroid carcinoma. There may also be questions regarding the need for ongoing monitoring. Screening for MTC presents challenges.

- Thyroid nodules are common (2-6% with palpation, 19-35% with ultrasound, 8-65% at autopsy [Dean 2008]). If liraglutide is approved, questions may arise regarding what a physician should do if a patient who is treated with liraglutide is found to have a thyroid nodule. Questions may also arise regarding when surgery is indicated for liraglutide-treated patients with thyroid nodules and/or elevated serum calcitonin values.
- A thyroid nodule that is associated with an elevated calcitonin might be more likely to go to surgery.
- Enhanced monitoring for thyroid nodules or elevated calcitonin could result in an increased rate of thyroidectomy. In the liraglutide development program, 14 liraglutide-treated patients had thyroidectomies, and 2 comparator-treated patients had thyroidectomies (ratio 3.5:1).
- Thyroidectomy has some known risks, such as recurrent laryngeal nerve injury with vocal cord dysfunction, hypoparathyroidism, hypothyroidism and anesthetic complications. Patients with diabetes may have a higher risk of postoperative complications in general, such as impaired wound healing. An increased likelihood of thyroidectomy, especially in patients with diabetes, might be considered a risk in itself.
- The applicant's risk management proposal does not recommend calcitonin measurements, thyroid ultrasound, or thyroid physical examination for patients prescribed liraglutide, if liraglutide is approved.

The following bullets summarize observations regarding papillary thyroid cancer.

- In clinical trials of liraglutide, there have been six cases of papillary thyroid carcinoma among liraglutide-treated patients, and one case in a comparator-treated patient (incidence ratio 3:1). At the time of submission of the NDA (when there were 4 LGT-treated cases), the rates for papillary thyroid carcinoma were 1.8 versus 0.9 events per 1000 patient-years for liraglutide versus comparator. Using updated exposure data, approximate rates would be 2.1 (6 cases over 2882 PY) versus 0.7 (1 case over 1486 PY), for an incidence rate ratio of 3:1.
- Five out of the six liraglutide-treated patients who had papillary thyroid carcinoma also had elevated calcitonin preoperatively, as did the single comparator-treated patient who had papillary thyroid carcinoma. The remaining liraglutide-treated patient who had papillary thyroid carcinoma had a thyroid nodule at baseline.

- Most of the reported papillary thyroid cancers were very small. Papillary microcarcinomata (<1 cm diameter) are common in the general population, and are often incidental findings. However, given the relatively short duration of observation in the liraglutide trials, and the often indolent nature of many thyroid cancers (papillary thyroid cancer in general, and many medullary thyroid cancers), large tumors might not be expected in the clinical trials, even if the tumors were drug-induced.
- Most of the cases of papillary thyroid cancer were discovered as a result of routine protocol-specified screening with calcitonin or ultrasound.
- Regarding the numerical imbalance in cases of papillary thyroid cancer, a question arises regarding whether liraglutide was inducing papillary thyroid cancer, or whether it was "inducing" thyroidectomies (for hypercalcitoninemia and/or thyroid nodules), with the subsequent incidental discovery of papillary microcarcinomata.
- Overall, it appears that most of these papillary cancers were incidental microcarcinomata discovered as a result of screening. However, ascertainment "bias" as a result of screening may not fully explain the numerical imbalance in cases, as patients in all treatment arms were screened, and thus similar percentages of incidental findings would have been expected between treatment arms.

7.1.3.3.3 Pancreatitis

Concern has arisen regarding spontaneous postmarketing reports of pancreatitis for Byetta® (exenatide), the only approved GLP-1 analogue. Therefore, pancreatitis is an adverse event of special interest for liraglutide. There is a numerical imbalance for cases of pancreatitis in the liraglutide development program. As of 4 March 2009, there had been 8 reported cases of pancreatitis in liraglutide-treated patients, and 1 among comparator-treated patients. These represent incidences of 0.19% and 0.04%, and rates per 1000 patient-years of 2.2 and 0.6, respectively.

The following table displays information regarding these cases of pancreatitis.

Table 7.1.3.3.3: Summary of Pancreatitis Cases, Liraglutide Development Program as of 4 March 2009

Study	Pt ID	Age (yrs)	Gender	Tx	Preferred Term	Risk Factors	Outcome	Latency[1] (days)
1573	117006	62	F	LGT 1.8 mg	Pancreatitis acute	HLP, cholelithiasis	Death	669
1572	162009	49	M	LGT 1.2 mg	Pancreatitis		Recovered; withdrawn from study	50
1573	120006	46	F	LGT 1.2 mg	Pancreatitis	EtOH	Recovered; temporary discontinuation from study	197
1573	514014	71	F	LGT 1.8 mg	Edematous pancreatitis	Cholecystitis, cholelithiasis	Ccty performed 1 week after pancreatitis;	313

Table 7.1.3.3.3: Summary of Pancreatitis Cases, Liraglutide Development Program as of 4 March 2009

Study	Pt ID	Age (yrs)	Gender	Tx	Preferred Term	Risk Factors	Outcome	Latency[1] (days)
							recovered; withdrawn from study	
NN8022-1807	132006	42	F	LGT 3.0 mg	Pancreatitis acute	Cholelithiasis	Recovered; withdrawn from study	299
1797	xx9001	64	M	LGT 1.8 mg	Pancreatitis acute		Recovered; withdrawn from study	419
1436	506016	63	M	LGT 0.6 mg	Pancreatitis chronic		Not recovered; continued in study	157
1797	204001	69	M	LGT 1.8 mg	Pancreatitis chronic		Not recovered; continued in study	88
1572	326013	58	F	GLIM + MET	Pancreatitis acute	TG >1500 mg/dL	Recovered; withdrawn from study	63

Source: Applicant's Tables 7-10 and 7-11, beg pg 91 (and text beginning pg 89), NDA 22341 Advisory Committee briefing document, submitted 4 Mar 2009
Abbreviations: Ccty = cholecystectomy; EtOH = ethanol use; HLP = hyperlipoproteinemia; TG = triglycerides; Tx = treatment
1 Time from onset of treatment to occurrence of pancreatitis

Brief narratives of these cases follow.

Patient 117006 was a 64 year old woman who had acute pancreatitis listed as her cause of death at autopsy. Please see Section 7.1.1 for a narrative regarding her death.

Patient 120006 was a 46 year old woman who received LGT 1.2 mg for 197 days. The narrative states that the patient drank approximately 5 alcoholic beverages per week. She had nonserious events of abdominal pain on Study Days 16 and 51. On Study Day 197, she was hospitalized for pancreatitis. After hospitalization, she underwent endoscopic retrograde cholecystopancreatography (ERCP), which was "unremarkable". Amylase and lipase were reported as elevated (values not reported). Three days later, she was recovered and discharged to home with normal amylase and lipase. Liraglutide was held during the event, but was resumed on discharge.

Patient 514014 was a 71 year old woman who received liraglutide 1.8 mg for 313 days. She did not have a history of alcohol abuse. On Study Day 313, she was hospitalized for severe abdominal pain and bilious vomiting. She was diagnosed with cholecystitis. Serum amylase was elevated at 1,651 U/L (ULN 53) and alanine aminotransferase (ALT) was elevated at 121 U/L (ULN 31). White blood cell count was elevated at 24,800 cells/μL (ULN 10,200). Ultrasound of right upper quadrant was consistent with pancreatitis and revealed biliary "mud". Abdominal CT was reported as Balthazar grade C, but with a CT severity index of 4 points. (This would indicate that the patient had pancreatic gland abnormalities and peripancreatic

inflammation on CT, for 2 points, plus 1-30% necrosis, for 2 additional points- reference Balthazar 1990). No gallstones were noted in the common bile duct. After 6 days of hospitalization, she was improved and tolerated a soft diet. Three days later, she underwent laparoscopic cholecystectomy and had multiple stones in the gallbladder, with no abnormalities on biliary exploration. She was discharged to home 1 day after cholecystectomy. Liraglutide was permanently discontinued.

Patient 162009 was a 49 year old man who received liraglutide 1.2 mg for 50 days. He had no history of alcohol abuse. On Study Day 51, he developed severe epigastric pain and nausea. Amylase was elevated (value not given), but abdominal ultrasound was normal. Abdominal CT revealed only fatty liver. A diagnosis of idiopathic pancreatitis was given based on the clinical history and elevated amylase. He recovered after 4 days. Liraglutide was permanently discontinued.

Patient 506016 was a 61 year old man who received liraglutide 0.6 mg for 157 days. He had a history of alcohol use ("50 grams daily"). On Study Day 99, he reported nausea, "acid dyspepsia", retrosternal burning, flatulence, bloating and weakness. After 25 more days, he was hospitalized, and diagnosed with worsening of gastroesophageal reflux disease and chronic pancreatitis. Amylase was reported as elevated at 119 U/L (ULN for assay not given). Seven days after admission, a CT of the pancreas showed no abnormalities and no calcification. Liraglutide was continued.

Patient 204001 was a 69 year old man who received liraglutide 1.8 mg for 88 days. On Study Day 88, he was diagnosed with chronic pancreatitis, but no laboratory or imaging results were provided. Liraglutide was continued, but the patient was later withdrawn from study due to lung cancer.

Patient 132006 was a 42 year old woman who received liraglutide 3.0 mg for 299 days, in an obesity trial. On Study Day 299, she was hospitalized for abdominal pain. She had elevated blood amylase, ALT, bilirubin and alkaline phosphatase (values not given). One day later, ultrasound showed gallstones, with normal bile duct and pancreas. Magnetic resonance cholangiopancreatography showed normal bile ducts. She was discharged after 6 days of hospitalization. Liraglutide was not discontinued.

Patient xx9001 did not appear to have a narrative in the original NDA submission, 120-day safety update, or Advisory Committee briefing document. In Table 7-11 of the Advisory Committee briefing document, the information states that the patient was a 64 year old man who had a diagnosis of "pancreatitis acute", a peak amylase level of 538 U/L (ULN 128), and a lipase of 1540 U/L (ULN 57). On CT scan, there was peripancreatic inflammatory fat stranding involving the distal pancreatic body and tail. Ultrasound showed minimal debris in the gallbladder but no stones. The patient recovered from the pancreatitis but was withdrawn from study.

Patient 326013 was a 58 year old woman who received glimepiride and metformin (but not liraglutide) for 63 days. She had no prior history of alcohol abuse. On Study Day 61, she presented with abdominal pain, nausea and vomiting, and she was hospitalized on Study Day 63.

Admission amylase was >2,000 U/L (ULN for assay not reported) and bilirubin was 19.9 µmol/L. Abdominal ultrasound and CT "showed signs of acute pancreatitis". The patient recovered and was discharged 6 days after admission. Liraglutide was permanently discontinued.

Overall, there was an imbalance in the occurrence of pancreatitis cases, with 8/4211 (0.19%) of LGT group patients and 1/2272 (0.04%) of comparator group patients having an event. The comparator group patient, and four of the LGT group patients, had risk factors for pancreatitis, such as cholelithiasis or alcohol abuse. Two patients had some evidence of necrosis (Patient 117006 at autopsy, and Patient 514014 on CT). One of the pancreatitis cases (117006) was fatal in the liraglutide group, although there were confounding elements of a colonoscopy shortly prior to the patient's death, and the fact that the pancreatitis was discovered only on autopsy after an unexplained out-of-hospital death. Pancreatitis may be a class effect for GLP-1 analogues, given recent findings with exenatide, for which final labeling language and placement is under discussion. If liraglutide is approved, a discussion of pancreatitis findings should be included in labeling, and the placement should be the same as that in the final exenatide label.

7.1.3.3.4 Fractures

In recent large, longterm trials of thiazolidinediones, an increased incidence of fractures was noted, particularly of the small bones of the extremities, especially in women. As mentioned in Section 7.1.2 above, the incidence of serious adverse events of fractures was similar for liraglutide-treated patients and comparator-treated patients. The following table displays the incidence of all events of fractures (serious + nonserious), for all completed trials of liraglutide at the time of the original NDA submission (23 May 2008).

Table 7.1.3.3.4: Fracture Events, All Completed Trials of Liraglutide at Time of NDA Submission

Preferred Term	PBO N=1122 n (%)	AC N=1165 n (%)	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)
Wrist fracture		3 (0.3)	3 (0.1)	2 (<0.1)
Rib fracture				5 (0.1)
Ankle fracture	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.1)
Hand fracture		2 (0.2)	2 (0.1)	2 (<0.1)
Foot fracture		1 (0.1)	1 (<0.1)	2 (<0.1)
Upper limb fracture		1 (0.1)	1 (<0.1)	1 (<0.1)
Radius fracture		1 (0.1)	1 (<0.1)	1 (<0.1)
Humerus fracture		1 (0.1)	1 (<0.1)	1 (<0.1)
Hip fracture		1 (0.1)	1 (<0.1)	1 (<0.1)
Traumatic fracture				1 (<0.1)
Tibia fracture	1 (0.1)		1 (<0.1)	
Pelvic fracture	1 (0.1)		1 (<0.1)	
Patella fracture	1 (0.1)		1 (<0.1)	
Open fracture	1 (0.1)		1 (<0.1)	
Lower limb fracture				1 (<0.1)
Femur fracture		1 (0.1)	1 (<0.1)	
Facial bones fracture				1 (<0.1)

Source: NDA 22341, submission 16 Jan 2009, Table 1-2, beg pg 66 of submission

Fractures do not appear to have occurred at a higher rate for liraglutide than for comparator.

7.1.3.3.5 Hypoglycemia

In theory, GLP-1-based therapies for diabetes might be expected to have a low risk for hypoglycemia, due to the fact that GLP-1 induces glucose-dependent insulin secretion. This is different from the sulfonylureas, which induce glucose-independent insulin secretion, and are associated with an increased risk of hypoglycemia.

In clinical trials of diabetes drugs, hypoglycemia is often divided into nonserious and serious hypoglycemia, with a serious hypoglycemic episode being defined as one in which the patient requires the assistance of another person in order to treat the hypoglycemia.

Regarding nonserious hypoglycemia, liraglutide was associated with fewer episodes than was glimepiride, a sulfonylurea, in the monotherapy Trial 1573 and in the add-on dual therapy Trial 1572. Nonserious hypoglycemia occurred with equal frequency between liraglutide and glargine insulin in Study 1697. Liraglutide was associated with more nonserious hypoglycemia than was rosiglitazone in Study 1436. These findings should be interpreted in the context of the efficacy results; please see Dr. Yanoff's review for details. The following table displays the incidence of nonserious hypoglycemia in these trials and their extensions.

Table 7.1.3.3.5.1: Percentage of Patients Who Experienced Nonserious Hypoglycemia, and Rate[1] per 1000 Patient-Years, Phase 3 Trials of Liraglutide

Study	LGT 1.2		LGT 1.8		PBO		AC	
	%	Rate	%	Rate	%	Rate	%	Rate
Study 1573 through 52 wks (mono vs. GLIM)	11.6	241.6	7.7	230.1	n/a	n/a	25.0	1659.2
Study 1573 through 104 weeks	12.0	210.0	10.2	220.0	n/a	n/a	26.2	1750.0
Study 1572 through 26 weeks (add-on to MET; AC = GLIM)	3.3	44.3	3.3	45.4	2.5	64.4	22.3	874.2
Study 1572 through 104 weeks	4.2	77.0	4.1	68.0	2.5	55.0	24.0	864.0
Study 1436 (add-on to SU; AC = RSG)	9.2	505.5	8.1	472.3	2.6	169.8	4.3	124.3
Study 1574 (add-on to MET + SU)	9.0	370.1	6.7	614.3	4.6	153.2	n/a	n/a
Study 1697 (add-on to MET + SU; AC = glargine insulin)	n/a	n/a	27.4	1156.1	16.7	945.9	28.9	1286.6

Source: Applicant's Table 6, pg 33, NDA 22341 submission stamp date 18 May 2009. Trial cut-off date for extensions not specified in applicant's table
1 Rate calculated as number of episodes divided by subject-years multiplied by 1000. Some patients had more than one episode; see source table

The rate of serious hypoglycemia was low, but all cases in the five major Phase 3 trials occurred among liraglutide-treated patients. There were 9 on-treatment cases of serious hypoglycemia for liraglutide, and none for either placebo or active comparator arms. In addition, in Study 1572, another patient treated with liraglutide 0.6 mg/day had a serious hypoglycemic episode one day after discontinuation of liraglutide. The following table displays the incidence and rate of major hypoglycemia in the five major Phase 3 trials.

Table 7.1.3.3.5.2: Percentage of Patients Who Experienced Serious Hypoglycemia, and Rate[1] per 1000 Patient-Years, Five Major Phase 3 Trials of Liraglutide

Study	LGT 1.2		LGT 1.8		PBO		AC	
	n(%)	Rate	n(%)	Rate	n(%)	Rate	n(%)	Rate
Study 1573 through 52 wks (mono vs. GLIM)	0	0	0	0	n/a	n/a	0	0
Study 1573 extension through 104 weeks	0	0	1 (0.4)	3.1	n/a	n/a	0	0
Study 1572 through 26 weeks (add-on to MET; AC = GLIM)	1 (0.4)	3.7	0	0	0	0	0	0
Study 1572 extension through 104 weeks	1 (0.4)	1.0	0	0	0	0	0	0
Study 1436 (add-on to SU; AC = RSG)	0	0	1 (0.4)	9.1	0	0	0	0
Study 1574 (add-on to MET + SU)	0	0	0	0	0	0	n/a	n/a
Study 1697 (add-on to MET + SU; AC = glargine insulin)	n/a	n/a	5 (2.2)	55.9	0	0	0	0

Source: Applicant's Table 6, pg 33, NDA 22341 submission stamp date 18 May 2009. Trial cut-off date for extensions not specified in applicant's table
1 Rate calculated as number of episodes divided by subject-years multiplied by 1000. In Study 1572, one patient had 3 serious episodes. In Study 1697, one patient had 2 serious episodes., and the other 4 patients had one serious episode

In six of nine cases of serious hypoglycemia, liraglutide had been coadministered with a sulfonylurea. In one case, the patient was receiving liraglutide, 1.8 mg as monotherapy. In two cases, the patients were receiving liraglutide in combination with metformin.

It is likely that this risk of serious hypoglycemia is similar between liraglutide and exenatide. The applicant recently submitted preliminary safety results from Study 1797, a trial of liraglutide versus exenatide. In that study and its extension up to the time of reporting (18 May 2009), there had been one case of serious hypoglycemia with liraglutide and two with exenatide. The full study report has not yet been submitted for review.

For other drugs, in some studies in which the rate of hypoglycemia was higher for the drug than for comparator, the rate of accidental injury was higher among patients treated with the drug. The clinical safety reviewer examined all accidents and injuries that were reported, and liraglutide did not appear to be associated with a higher incidence of accidents or injuries than comparator (4.4% LGT versus 5.9% comparator, source NDA 22341 submission receipt date 16 Jan 2009).

7.1.4 Other Search Strategies

As described in Section 7.1.3.3, search strategies involving use of MedDRA Standardized Queries were used for the evaluation of major adverse cardiovascular events.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the major Phase 3 trials of liraglutide, patients were asked about adverse events with the question "Have you experienced any problems since the last contact?".

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events in the major Phase 3 trials were coded using MedDRA Version 10.1. Explorations of verbatim investigator terms and assigned Preferred Terms did not reveal evidence of miscategorization of events. Explorations for "splitting" and "lumping" of terms were conducted, and *post hoc* event grouping was performed where splitting seemed possible. There was no evidence of systematic incorrect assignment of adverse event terms.

7.1.5.3 Incidence of common adverse events

Across the completed trials of liraglutide at the time of the NDA submission, adverse events occurred among 72% of liraglutide-treated patients and among 63% of comparator-treated patients. This difference was largely accounted for by gastrointestinal events, which occurred in 40% of liraglutide-treated patients, but in only 20% of comparator-treated patients.

7.1.5.4 Common adverse event tables

In the original NDA submission, the applicant did not submit a consolidated tabular presentation of all adverse events by MedDRA System Organ Class and Preferred Term for the set of all completed trials of liraglutide. Serious adverse events had been submitted, but not all adverse events. On 16 Dec 2008, the Division requested that the applicant submit those data in table format. On 16 Jan 2009, the applicant submitted this information, in the form of a 100 page table, to the NDA. Tables in this section are derived from that submission.

The following table summarizes those adverse events which occurred in at least 1% of patients in a liraglutide treatment group (and in at least 2 patients in a liraglutide treatment group), and which occurred with numerically higher incidence in a liraglutide treatment group than in a comparator group.

Table 7.1.5.4.1: Incidence of Adverse Events (Serious + Nonserious) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission. Events Which Occurred in at Least 1% of Patients in a Liraglutide Dose Group (and in at Least 2 Patients in a Liraglutide Dose Group) and Which Occurred at a Higher Numerical Rate for a Liraglutide Dose Group than for a Comparator Group

System Organ Class	Preferred Term	PBO N=1122 n (%)	AC N=1165 n (%)	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)	LGT <0.6 N=401 n (%)	LGT 0.6 N=641 n (%)	LGT >0.6-<1.2 N=416 n (%)	LGT 1.2 N=993 n (%)	LGT >1.2-<1.8 N=64 n (%)	LGT 1.8 N=1408 n (%)	LGT >1.8 N=288 n (%)
Any	Any	675 (60.2)	767 (65.8)	1437 (63.2)	3015 (71.6)	220 (54.9)	451 (70.4)	209 (50.2)	785 (79.1)	32 (50.0)	1082 (76.8)	236 (81.9)
Gastrointestinal disorders	Any	212 (18.9)	246 (21.1)	455 (20.0)	1682 (39.9)	65 (16.2)	209 (32.6)	109 (26.2)	447 (45.0)	21 (32.8)	658 (46.7)	173 (60.1)
	Nausea	56 (5.0)	48 (4.1)	102 (4.5)	788 (18.7)	21 (5.2)	53 (8.3)	60 (14.4)	210 (21.1)	7 (10.9)	341 (24.2)	96 (33.3)
	Diarrhea	54 (4.8)	72 (6.2)	126 (5.5)	437 (10.4)	15 (3.7)	51 (8.0)	24 (5.8)	108 (10.9)	10 (15.6)	183 (13.0)	46 (16.0)
	Vomiting	25 (2.2)	20 (1.7)	45 (2.0)	285 (6.8)	5 (1.2)	20 (3.1)	23 (5.5)	76 (7.7)	9 (14.1)	124 (8.8)	28 (9.7)
	Constipation	25 (2.2)	32 (2.7)	57 (2.5)	234 (5.6)	11 (2.7)	22 (3.4)	11 (2.6)	67 (6.7)	3 (4.7)	86 (6.1)	34 (11.8)
	Dyspepsia	10 (0.9)	22 (1.9)	32 (1.4)	191 (4.5)	6 (1.5)	20 (3.1)	5 (1.2)	40 (4.0)	3 (4.7)	91 (6.5)	26 (9.0)
	Abdominal pain	24 (2.1)	22 (1.9)	46 (2.0)	86 (2.0)	5 (1.2)	10 (1.6)	10 (2.4)	18 (1.8)	2 (3.1)	37 (2.6)	4 (1.4)
	Abdominal pain upper	9 (0.8)	18 (1.5)	27 (1.2)	94 (2.2)	3 (0.7)	9 (1.4)	3 (0.7)	28 (2.8)		39 (2.8)	12 (4.2)
	Flatulence	11 (1.0)	16 (1.4)	27 (1.2)	68 (1.6)	1 (0.2)	6 (0.9)	1 (0.2)	11 (1.1)		39 (2.8)	10 (3.5)
	Toothache	11 (1.0)	19 (1.6)	30 (1.3)	57 (1.4)	2 (0.5)	12 (1.9)	2 (0.5)	18 (1.8)		22 (1.6)	1 (0.3)
	Abdominal distension	10 (0.9)	9 (0.8)	19 (0.8)	62 (1.5)	1 (0.2)	8 (1.2)	2 (0.5)	22 (2.2)		24 (1.7)	5 (1.7)
	Gastritis	2 (0.2)	9 (0.8)	11 (0.5)	60 (1.4)	2 (0.5)	12 (1.9)	3 (0.7)	18 (1.8)		25 (1.8)	
	Gastroesophageal reflux disease	2 (0.2)	6 (0.5)	8 (0.4)	48 (1.1)	1 (0.2)	8 (1.2)	1 (0.2)	12 (1.2)		20 (1.4)	6 (2.1)
	Abdominal discomfort	4 (0.4)	7 (0.6)	11 (0.5)	37 (0.9)		9 (1.4)	2 (0.5)	9 (0.9)		14 (1.0)	3 (1.0)
	Eructation	1 (0.1)	3 (0.3)	4 (0.2)	45 (1.1)		3 (0.5)		8 (0.8)		26 (1.8)	8 (2.8)
	Stomach discomfort	8 (0.7)	1 (0.1)	9 (0.4)	31 (0.7)	3 (0.7)	3 (0.5)	5 (1.2)	4 (0.4)		14 (1.0)	2 (0.7)
	Dry mouth	3 (0.3)	2 (0.2)	5 (0.2)	36 (0.9)	1 (0.2)	7 (1.1)		6 (0.6)		15 (1.1)	7 (2.4)
	Feces hard	1 (0.1)		1 (<0.1)	8 (0.2)						4 (0.3)	4 (1.4)
Infections and infestations	Any	302 (26.9)	389 (33.4)	691 (30.4)	1281 (30.4)	69 (17.2)	214 (33.4)	49 (11.8)	381 (38.4)	5 (7.8)	465 (33.0)	98 (34.0)
	Nasopharyngitis	98 (8.7)	108 (9.3)	206 (9.1)	373 (8.9)	27 (6.7)	66 (10.3)	18 (4.3)	88 (8.9)		142 (10.1)	32 (11.1)
	Upper respiratory tract infection	48 (4.3)	54 (4.6)	102 (4.5)	229 (5.4)	15 (3.7)	43 (6.7)	10 (2.4)	76 (7.7)	1 (1.6)	71 (5.0)	13 (4.5)
	Influenza	23 (2.0)	54 (4.6)	77 (3.4)	130 (3.1)		16 (2.5)		41 (4.1)	2 (3.1)	61 (4.3)	10 (3.5)
	Gastroenteritis	13 (1.2)	30 (2.6)	43 (1.9)	108 (2.6)	1 (0.2)	17 (2.7)	1 (0.2)	32 (3.2)		41 (2.9)	16 (5.6)
	Bronchitis	15 (1.3)	36 (3.1)	51 (2.2)	85 (2.0)	1 (0.2)	15 (2.3)	1 (0.2)	32 (3.2)	1 (1.6)	32 (2.3)	3 (1.0)
	Urinary tract infection	13 (1.2)	21 (1.8)	34 (1.5)	88 (2.1)	3 (0.7)	12 (1.9)	1 (0.2)	42 (4.2)		27 (1.9)	3 (1.0)

Table 7.1.5.4.1: Incidence of Adverse Events (Serious + Nonserious) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission. Events Which Occurred in at Least 1% of Patients in a Liraglutide Dose Group (and in at Least 2 Patients in a Liraglutide Dose Group) and Which Occurred at a Higher Numerical Rate for a Liraglutide Dose Group than for a Comparator Group

System Organ Class	Preferred Term	PBO N=1122 n (%)	AC N=1165 n (%)	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)	LGT <0.6 N=401 n (%)	LGT 0.6 N=641 n (%)	LGT >0.6-<1.2 N=416 n (%)	LGT 1.2 N=993 n (%)	LGT >1.2-<1.8 N=64 n (%)	LGT 1.8 N=1408 n (%)	LGT >1.8 N=288 n (%)
	Sinusitis	13 (1.2)	27 (2.3)	40 (1.8)	75 (1.8)	7 (1.7)	10 (1.6)	3 (0.7)	28 (2.8)	1 (1.6)	25 (1.8)	1 (0.3)
	Pharyngitis	18 (1.6)	17 (1.5)	35 (1.5)	55 (1.3)	5 (1.2)	11 (1.7)	4 (1.0)	13 (1.3)	1 (1.6)	19 (1.3)	2 (0.7)
	Gastroenteritis viral	3 (0.3)	9 (0.8)	12 (0.5)	36 (0.9)	1 (0.2)	2 (0.3)		14 (1.4)		18 (1.3)	1 (0.3)
	Tooth infection	8 (0.7)	16 (1.4)	24 (1.1)	30 (0.7)		7 (1.1)		8 (0.8)		11 (0.8)	4 (1.4)
	Rhinitis	8 (0.7)	12 (1.0)	20 (0.9)	28 (0.7)	4 (1.0)	4 (0.6)	5 (1.2)	2 (0.2)	1 (1.6)	11 (0.8)	1 (0.3)
	Viral infection	6 (0.5)	10 (0.9)	16 (0.7)	28 (0.7)		7 (1.1)		10 (1.0)		11 (0.8)	
Nervous system disorders	Any	189 (16.8)	184 (15.8)	371 (16.3)	786 (18.7)	63 (15.7)	90 (14.0)	73 (17.5)	195 (19.6)	12 (18.8)	295 (21.0)	58 (20.1)
	Headache	133 (11.9)	106 (9.1)	239 (10.5)	471 (11.2)	36 (9.0)	52 (8.1)	48 (11.5)	105 (10.6)	9 (14.1)	179 (12.7)	42 (14.6)
	Dizziness	36 (3.2)	25 (2.1)	60 (2.6)	172 (4.1)	19 (4.7)	19 (3.0)	27 (6.5)	35 (3.5)	3 (4.7)	61 (4.3)	8 (2.8)
	Dizziness postural	2 (0.2)		2 (0.1)	12 (0.3)	5 (1.2)	2 (0.3)	2 (0.5)	1 (0.1)		2 (0.1)	
Musculoskeletal and connective tissue disorders	Any	117 (10.4)	188 (16.1)	304 (13.4)	532 (12.6)	23 (5.7)	84 (13.1)	23 (5.5)	163 (16.4)	5 (7.8)	204 (14.5)	30 (10.4)
	Back pain	27 (2.4)	50 (4.3)	77 (3.4)	147 (3.5)	5 (1.2)	24 (3.7)	6 (1.4)	43 (4.3)	1 (1.6)	59 (4.2)	9 (3.1)
	Arthralgia	19 (1.7)	41 (3.5)	60 (2.6)	64 (1.5)	4 (1.0)	13 (2.0)	3 (0.7)	17 (1.7)	1 (1.6)	23 (1.6)	3 (1.0)
	Pain in extremity	16 (1.4)	21 (1.8)	37 (1.6)	77 (1.8)	2 (0.5)	9 (1.4)	1 (0.2)	20 (2.0)		41 (2.9)	4 (1.4)
	Myalgia	11 (1.0)	21 (1.8)	32 (1.4)	50 (1.2)	3 (0.7)	7 (1.1)	4 (1.0)	12 (1.2)		23 (1.6)	1 (0.3)
	Musculoskeletal pain	12 (1.1)	14 (1.2)	26 (1.1)	50 (1.2)		6 (0.9)	2 (0.5)	18 (1.8)		20 (1.4)	4 (1.4)
	Osteoarthritis	6 (0.5)	11 (0.9)	17 (0.7)	24 (0.6)		9 (1.4)		6 (0.6)		8 (0.6)	1 (0.3)
	Neck pain	2 (0.2)	9 (0.8)	11 (0.5)	21 (0.5)		4 (0.6)		10 (1.0)		7 (0.5)	
General disorders and administration site conditions	Any	99 (8.8)	97 (8.3)	195 (8.6)	514 (12.2)	36 (9.0)	64 (10.0)	28 (6.7)	132 (13.3)	5 (7.8)	199 (14.1)	50 (17.4)
	Fatigue	19 (1.7)	17 (1.5)	36 (1.6)	136 (3.2)	11 (2.7)	12 (1.9)	4 (1.0)	27 (2.7)	2 (3.1)	63 (4.5)	17 (5.9)
	Pyrexia	8 (0.7)	12 (1.0)	20 (0.9)	53 (1.3)	2 (0.5)	7 (1.1)	1 (0.2)	17 (1.7)		24 (1.7)	2 (0.7)
	Asthenia	5 (0.4)	5 (0.4)	10 (0.4)	40 (0.9)	1 (0.2)	3 (0.5)	2 (0.5)	13 (1.3)	1 (1.6)	18 (1.3)	2 (0.7)
	Injection site bruising	10 (0.9)	3 (0.3)	13 (0.6)	32 (0.8)	5 (1.2)	8 (1.2)		5 (0.5)		7 (0.5)	7 (2.4)
	Pain	2 (0.2)	6 (0.5)	8 (0.4)	25 (0.6)	4 (1.0)	8 (1.2)	1 (0.2)	5 (0.5)		7 (0.5)	
	Malaise	2 (0.2)	3 (0.3)	5 (0.2)	24 (0.6)	2 (0.5)	1 (0.2)	1 (0.2)	5 (0.5)	2 (3.1)	10 (0.7)	3 (1.0)
	Injection site rash				17 (0.4)		2 (0.3)		5 (0.5)	1 (1.6)	6 (0.4)	3 (1.0)
	Injection site irritation	1 (0.1)	2 (0.2)	3 (0.1)	12 (0.3)				2 (0.2)		6 (0.4)	4 (1.4)
	Injection site inflammation		1 (0.1)	1 (<0.1)	9 (0.2)	4 (1.0)	1 (0.2)	2 (0.5)	2 (0.2)			

Table 7.1.5.4.1: Incidence of Adverse Events (Serious + Nonserious) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission. Events Which Occurred in at Least 1% of Patients in a Liraglutide Dose Group (and in at Least 2 Patients in a Liraglutide Dose Group) and Which Occurred at a Higher Numerical Rate for a Liraglutide Dose Group than for a Comparator Group

System Organ Class	Preferred Term	PBO N=1122 n (%)	AC N=1165 n (%)	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)	LGT <0.6 N=401 n (%)	LGT 0.6 N=641 n (%)	LGT >0.6-<1.2 N=416 n (%)	LGT 1.2 N=993 n (%)	LGT >1.2-<1.8 N=64 n (%)	LGT 1.8 N=1408 n (%)	LGT >1.8 N=288 n (%)
Metabolism and nutrition disorders	Any	75 (6.7)	81 (7.0)	156 (6.9)	483 (11.5)	24 (6.0)	47 (7.3)	10 (2.4)	145 (14.6)	1 (1.6)	230 (16.3)	26 (9.0)
	Decreased appetite	9 (0.8)	1 (0.1)	10 (0.4)	152 (3.6)	1 (0.2)	5 (0.8)	1 (0.2)	46 (4.6)		96 (6.8)	3 (1.0)
	Anorexia	8 (0.7)	7 (0.6)	15 (0.7)	137 (3.3)	4 (1.0)	9 (1.4)	3 (0.7)	35 (3.5)		77 (5.5)	9 (3.1)
	Dyslipidemia	15 (1.3)	13 (1.1)	28 (1.2)	40 (0.9)		9 (1.4)		14 (1.4)		15 (1.1)	2 (0.7)
	Hyperlipidemia	9 (0.8)	15 (1.3)	24 (1.1)	31 (0.7)	3 (0.7)	4 (0.6)	1 (0.2)	10 (1.0)		13 (0.9)	
	Hyperglycemia	16 (1.4)	4 (0.3)	20 (0.9)	25 (0.6)	7 (1.7)	3 (0.5)	2 (0.5)	6 (0.6)		7 (0.5)	
	Hypertriglyceridemia		14 (1.2)	14 (0.6)	28 (0.7)	5 (1.2)	2 (0.3)	1 (0.2)	8 (0.8)		11 (0.8)	1 (0.3)
	Hypoglycemia	1 (0.1)		1 (<0.1)	10 (0.2)	1 (0.2)	1 (0.2)		1 (0.1)		4 (0.3)	3 (1.0)
	Hyperinsulinism	2 (0.2)	2 (0.2)	4 (0.2)	6 (0.1)				2 (0.2)		1 (0.1)	3 (1.0)
Respiratory, thoracic and mediastinal disorders	Any	61 (5.4)	76 (6.5)	137 (6.0)	252 (6.0)	20 (5.0)	40 (6.2)	15 (3.6)	75 (7.6)	3 (4.7)	90 (6.4)	9 (3.1)
	Cough	26 (2.3)	34 (2.9)	60 (2.6)	73 (1.7)	3 (0.7)	16 (2.5)	1 (0.2)	24 (2.4)		26 (1.8)	3 (1.0)
	Pharyngolaryngeal pain	9 (0.8)	18 (1.5)	27 (1.2)	61 (1.4)	2 (0.5)	7 (1.1)	4 (1.0)	17 (1.7)	1 (1.6)	27 (1.9)	3 (1.0)
	Upper respiratory tract inflammation				7 (0.2)	6 (1.5)		1 (0.2)				
Investigations	Any	61 (5.4)	70 (6.0)	131 (5.8)	227 (5.4)	9 (2.2)	45 (7.0)	3 (0.7)	68 (6.8)		94 (6.7)	8 (2.8)
	Blood calcitonin increased	5 (0.4)	5 (0.4)	10 (0.4)	25 (0.6)		8 (1.2)		6 (0.6)		11 (0.8)	
Injury, poisoning and procedural complications	Any	41 (3.7)	93 (8.0)	134 (5.9)	204 (4.8)	6 (1.5)	34 (5.3)	11 (2.6)	62 (6.2)	2 (3.1)	75 (5.3)	14 (4.9)
	Fall	4 (0.4)	9 (0.8)	13 (0.6)	25 (0.6)	1 (0.2)	7 (1.1)	2 (0.5)	7 (0.7)		8 (0.6)	
	Injury	4 (0.4)	4 (0.3)	8 (0.4)	9 (0.2)	1 (0.2)		4 (1.0)			2 (0.1)	2 (0.7)
Skin and subcutaneous tissue disorders	Any	49 (4.4)	53 (4.5)	102 (4.5)	236 (5.6)	9 (2.2)	35 (5.5)	12 (2.9)	74 (7.5)	2 (3.1)	89 (6.3)	15 (5.2)
	Rash	12 (1.1)	14 (1.2)	26 (1.1)	50 (1.2)	2 (0.5)	6 (0.9)	1 (0.2)	15 (1.5)	1 (1.6)	23 (1.6)	2 (0.7)
	Hyperhidrosis	6 (0.5)	3 (0.3)	9 (0.4)	15 (0.4)	1 (0.2)	3 (0.5)	1 (0.2)	2 (0.2)		5 (0.4)	3 (1.0)
	Dry skin	1 (0.1)		1 (<0.1)	11 (0.3)		2 (0.3)		3 (0.3)		3 (0.2)	3 (1.0)
Eye disorders	Any	41 (3.7)	52 (4.5)	93 (4.1)	173 (4.1)	7 (1.7)	35 (5.5)	4 (1.0)	57 (5.7)		62 (4.4)	8 (2.8)
	Diabetic retinopathy	7 (0.6)	16 (1.4)	23 (1.0)	38 (0.9)	1 (0.2)	11 (1.7)		14 (1.4)		12 (0.9)	
Vascular disorders	Any	26 (2.3)	57 (4.9)	83 (3.7)	160 (3.8)	9 (2.2)	31 (4.8)	11 (2.6)	42 (4.2)	1 (1.6)	56 (4.0)	10 (3.5)

Table 7.1.5.4.1: Incidence of Adverse Events (Serious + Nonserious) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission. Events Which Occurred in at Least 1% of Patients in a Liraglutide Dose Group (and in at Least 2 Patients in a Liraglutide Dose Group) and Which Occurred at a Higher Numerical Rate for a Liraglutide Dose Group than for a Comparator Group

System Organ Class	Preferred Term	PBO N=1122 n (%)	AC N=1165 n (%)	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)	LGT <0.6 N=401 n (%)	LGT 0.6 N=641 n (%)	LGT >0.6-<1.2 N=416 n (%)	LGT 1.2 N=993 n (%)	LGT >1.2-<1.8 N=64 n (%)	LGT 1.8 N=1408 n (%)	LGT >1.8 N=288 n (%)
	Hypertension	15 (1.3)	40 (3.4)	55 (2.4)	74 (1.8)	5 (1.2)	15 (2.3)	1 (0.2)	21 (2.1)	1 (1.6)	30 (2.1)	1 (0.3)
Psychiatric disorders	Any	31 (2.8)	39 (3.3)	68 (3.0)	147 (3.5)	4 (1.0)	18 (2.8)	3 (0.7)	38 (3.8)		66 (4.7)	18 (6.3)
	Insomnia	6 (0.5)	12 (1.0)	18 (0.8)	44 (1.0)	2 (0.5)	6 (0.9)	1 (0.2)	7 (0.7)		21 (1.5)	7 (2.4)
	Depression	6 (0.5)	10 (0.9)	16 (0.7)	40 (0.9)	1 (0.2)	2 (0.3)	1 (0.2)	15 (1.5)		20 (1.4)	1 (0.3)
	Anxiety	9 (0.8)	10 (0.9)	19 (0.8)	23 (0.5)		2 (0.3)		10 (1.0)		8 (0.6)	3 (1.0)
	Depressed mood				9 (0.2)				1 (0.1)		4 (0.3)	4 (1.4)
Cardiac disorders	Any	25 (2.2)	32 (2.7)	57 (2.5)	139 (3.3)	6 (1.5)	31 (4.8)	3 (0.7)	46 (4.6)	2 (3.1)	45 (3.2)	6 (2.1)
	Palpitations	4 (0.4)	5 (0.4)	9 (0.4)	27 (0.6)	2 (0.5)	2 (0.3)		6 (0.6)		12 (0.9)	5 (1.7)
	Angina pectoris	3 (0.3)	3 (0.3)	6 (0.3)	20 (0.5)		9 (1.4)	1 (0.2)	5 (0.5)	1 (1.6)	4 (0.3)	
Renal and urinary disorders[1]	Any	20 (1.8)	39 (3.3)	59 (2.6)	93 (2.2)	4 (1.0)	22 (3.4)	4 (1.0)	32 (3.2)		26 (1.8)	5 (1.7)
Reproductive system and breast disorders[1]	Any	11 (1.0)	22 (1.9)	33 (1.5)	69 (1.6)	5 (1.2)	11 (1.7)	2 (0.5)	19 (1.9)	2 (3.1)	26 (1.8)	4 (1.4)
Ear and labyrinth disorders	Any	10 (0.9)	18 (1.5)	28 (1.2)	58 (1.4)		5 (0.8)	3 (0.7)	18 (1.8)		27 (1.9)	5 (1.7)
	Vertigo	5 (0.4)	9 (0.8)	14 (0.6)	28 (0.7)		2 (0.3)	1 (0.2)	6 (0.6)		16 (1.1)	3 (1.0)
Blood and lymphatic system disorders	Any	9 (0.8)	13 (1.1)	22 (1.0)	54 (1.3)	4 (1.0)	11 (1.7)		23 (2.3)		16 (1.1)	
	Anemia	6 (0.5)	6 (0.5)	12 (0.5)	27 (0.6)	2 (0.5)	4 (0.6)		11 (1.1)		10 (0.7)	
Hepatobiliary disorders	Any	6 (0.5)	13 (1.1)	19 (0.8)	49 (1.2)	2 (0.5)	14 (2.2)	1 (0.2)	13 (1.3)		15 (1.1)	4 (1.4)
	Hepatic steatosis	3 (0.3)	7 (0.6)	10 (0.4)	23 (0.5)		8 (1.2)		7 (0.7)		5 (0.4)	3 (1.0)
Immune system disorders	Any	4 (0.4)	8 (0.7)	12 (0.5)	51 (1.2)	3 (0.7)	8 (1.2)	2 (0.5)	18 (1.8)	1 (1.6)	12 (0.9)	7 (2.4)
	Seasonal allergy		5 (0.4)	5 (0.2)	22 (0.5)	1 (0.2)	3 (0.5)	1 (0.2)	9 (0.9)	1 (1.6)	3 (0.2)	4 (1.4)
Neoplasms	Any	7 (0.6)	5 (0.4)	12 (0.5)	53 (1.3)	8 (2.0)	8 (1.2)	2 (0.5)	17 (1.7)		17 (1.2)	1 (0.3)
	Thyroid neoplasm	3 (0.3)	1 (0.1)	4 (0.2)	15 (0.4)	8 (2.0)	2 (0.3)	1 (0.2)	4 (0.4)			
Endocrine disorders[1]	Any	2 (0.2)	5 (0.4)	7 (0.3)	25 (0.6)		4 (0.6)		12 (1.2)		7 (0.5)	2 (0.7)
Surgical and medical procedures[1]	Any	3 (0.3)	9 (0.8)	12 (0.5)	18 (0.4)		4 (0.6)		8 (0.8)		5 (0.4)	1 (0.3)

Table 7.1.5.4.1: Incidence of Adverse Events (Serious + Nonserious) by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission. Events Which Occurred in at Least 1% of Patients in a Liraglutide Dose Group (and in at Least 2 Patients in a Liraglutide Dose Group) and Which Occurred at a Higher Numerical Rate for a Liraglutide Dose Group than for a Comparator Group

System Organ Class	Preferred Term	PBO N=1122 n (%)	AC N=1165 n (%)	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)	LGT <0.6 N=401 n (%)	LGT 0.6 N=641 n (%)	LGT >0.6-<1.2 N=416 n (%)	LGT 1.2 N=993 n (%)	LGT >1.2-<1.8 N=64 n (%)	LGT 1.8 N=1408 n (%)	LGT >1.8 N=288 n (%)
Congenital, familial and genetic disorders[1]	Any	1 (0.1)	2 (0.2)	3 (0.1)	4 (0.1)	1 (0.2)	1 (0.2)		1 (0.1)		1 (0.1)	

Source: NDA 22341 stamp date 16 Jan 2009, Table 1-2, beg pg 8
1 These System Organ Classes had no individual event terms which met criteria for inclusion in this table

In the above table, gastrointestinal events and injection site events appeared to occur with higher frequency among liraglutide-treated patients than among comparator-treated patients. Please see Section 7.1.11 for a discussion of malignancy events. This method of presentation of events may result in inclusion of events which are not related to liraglutide use; more specific presentations follow.

The following table includes events which occurred in at least 1% of patients in the pooled liraglutide group, and which occurred at a numerically higher incidence in the pooled liraglutide group than in the pooled comparator group.

Table 7.1.5.4.2: Events Which Occurred in at Least 1% of Patients in the Pooled Liraglutide Group, and Which Occurred at a Higher Numerical Frequency Among Patients in the Pooled Liraglutide Group than Among Patients in the Pooled Comparator Group

System Organ Class	Preferred Term	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)
Any	Any	1437 (63.2)	3015 (71.6)
Gastrointestinal disorders	Any	455 (20.0)	1682 (39.9)
	Nausea	102 (4.5)	788 (18.7)
	Diarrhea	126 (5.5)	437 (10.4)
	Vomiting	45 (2.0)	285 (6.8)
	Constipation	57 (2.5)	234 (5.6)
	Dyspepsia	32 (1.4)	191 (4.5)
	Abdominal pain upper	27 (1.2)	94 (2.2)
	Flatulence	27 (1.2)	68 (1.6)
	Toothache	30 (1.3)	57 (1.4)
	Abdominal distension	19 (0.8)	62 (1.5)
	Gastritis	11 (0.5)	60 (1.4)
	Gastroesophageal reflux disease	8 (0.4)	48 (1.1)
	Eructation	4 (0.2)	45 (1.1)
Infections and infestations	Any	691 (30.4)	1281 (30.4)
	Upper respiratory tract infection	102 (4.5)	229 (5.4)
	Gastroenteritis	43 (1.9)	108 (2.6)
	Urinary tract infection	34 (1.5)	88 (2.1)
Nervous system disorders	Any	371 (16.3)	786 (18.7)
	Headache	239 (10.5)	471 (11.2)
	Dizziness	60 (2.6)	172 (4.1)
Musculoskeletal and connective tissue disorders	Any	304 (13.4)	532 (12.6)
	Back pain	77 (3.4)	147 (3.5)
	Pain in extremity	37 (1.6)	77 (1.8)
	Musculoskeletal pain	26 (1.1)	50 (1.2)
General disorders and administration site conditions	Any	195 (8.6)	514 (12.2)
	Fatigue	36 (1.6)	136 (3.2)
	Pyrexia	20 (0.9)	53 (1.3)
Metabolism and nutrition disorders	Any	156 (6.9)	483 (11.5)
	Decreased appetite	10 (0.4)	152 (3.6)
	Anorexia	15 (0.7)	137 (3.3)
Respiratory, thoracic and mediastinal disorders	Any	137 (6.0)	252 (6.0)
	Pharyngolaryngeal pain	27 (1.2)	61 (1.4)
Skin and subcutaneous tissue disorders	Any	102 (4.5)	236 (5.6)
	Rash	26 (1.1)	50 (1.2)
Vascular disorders[1]	Any	83 (3.7)	160 (3.8)
Psychiatric disorders	Any	68 (3.0)	147 (3.5)
	Insomnia	18 (0.8)	44 (1.0)
Cardiac disorders[1]	Any	57 (2.5)	139 (3.3)
Reproductive system and breast disorders[1]	Any	33 (1.5)	69 (1.6)
Ear and labyrinth disorders[1]	Any	28 (1.2)	58 (1.4)
Blood and lymphatic system disorders[1]	Any	22 (1.0)	54 (1.3)
Hepatobiliary disorders[1]	Any	19 (0.8)	49 (1.2)
Immune system disorders[1]	Any	12 (0.5)	51 (1.2)
Neoplasms[1]	Any	12 (0.5)	53 (1.3)

Source: Table 7.1.5.4.1 above
1 These System Organ Classes had no individual event terms which met criteria for inclusion in this table

In the above table, gastrointestinal events occurred with higher numerical frequency among liraglutide-treated patients than among comparator-treated patients.

The following table includes events which occurred in at least 1% of patients in the pooled liraglutide group, and which occurred at a numerically higher incidence in the pooled liraglutide group than in both the pooled placebo and pooled active comparator groups.

Table 7.1.5.4.3: Incidence of Events Which Occurred in at Least 1% of Patients in the Pooled Liraglutide Group, and Which Occurred with Higher Numerical Frequency among Patients in the Pooled Liraglutide Group than in Patients in Both the Pooled Placebo and Pooled Active Comparator Groups

System Organ Class	Preferred Term	PBO N=1122 n (%)	AC N=1165 n (%)	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)
Any	Any	675 (60.2)	767 (65.8)	1437 (63.2)	3015 (71.6)
Gastrointestinal disorders	Any	212 (18.9)	246 (21.1)	455 (20.0)	1682 (39.9)
	Nausea	56 (5.0)	48 (4.1)	102 (4.5)	788 (18.7)
	Diarrhea	54 (4.8)	72 (6.2)	126 (5.5)	437 (10.4)
	Vomiting	25 (2.2)	20 (1.7)	45 (2.0)	285 (6.8)
	Constipation	25 (2.2)	32 (2.7)	57 (2.5)	234 (5.6)
	Dyspepsia	10 (0.9)	22 (1.9)	32 (1.4)	191 (4.5)
	Abdominal pain upper	9 (0.8)	18 (1.5)	27 (1.2)	94 (2.2)
	Flatulence	11 (1.0)	16 (1.4)	27 (1.2)	68 (1.6)
	Abdominal distension	10 (0.9)	9 (0.8)	19 (0.8)	62 (1.5)
	Gastritis	2 (0.2)	9 (0.8)	11 (0.5)	60 (1.4)
	Gastroesophageal reflux disease	2 (0.2)	6 (0.5)	8 (0.4)	48 (1.1)
	Abdominal discomfort	4 (0.4)	7 (0.6)	11 (0.5)	37 (0.9)
	Eructation	1 (0.1)	3 (0.3)	4 (0.2)	45 (1.1)
Infections and infestations	Any	302 (26.9)	389 (33.4)	691 (30.4)	1281 (30.4)
	Upper respiratory tract infection	48 (4.3)	54 (4.6)	102 (4.5)	229 (5.4)
	Urinary tract infection	13 (1.2)	21 (1.8)	34 (1.5)	88 (2.1)
Nervous system disorders	Any	189 (16.8)	184 (15.8)	371 (16.3)	786 (18.7)
	Dizziness	36 (3.2)	25 (2.1)	60 (2.6)	172 (4.1)
General disorders and administration site conditions	Any	99 (8.8)	97 (8.3)	195 (8.6)	514 (12.2)
	Fatigue	19 (1.7)	17 (1.5)	36 (1.6)	136 (3.2)
	Pyrexia	8 (0.7)	12 (1.0)	20 (0.9)	53 (1.3)
Metabolism and nutrition disorders	Any	75 (6.7)	81 (7.0)	156 (6.9)	483 (11.5)
	Decreased appetite	9 (0.8)	1 (0.1)	10 (0.4)	152 (3.6)
	Anorexia	8 (0.7)	7 (0.6)	15 (0.7)	137 (3.3)
Skin and subcutaneous tissue disorders[1]	Any	49 (4.4)	53 (4.5)	102 (4.5)	236 (5.6)
Psychiatric disorders[1]	Any	31 (2.8)	39 (3.3)	68 (3.0)	147 (3.5)
Cardiac disorders[1]	Any	25 (2.2)	32 (2.7)	57 (2.5)	139 (3.3)
Blood and lymphatic system disorders[1]	Any	9 (0.8)	13 (1.1)	22 (1.0)	54 (1.3)
Hepatobiliary disorders[1]	Any	6 (0.5)	13 (1.1)	19 (0.8)	49 (1.2)
Immune system disorders[1]	Any	4 (0.4)	8 (0.7)	12 (0.5)	51 (1.2)
Neoplasms[1]	Any	7 (0.6)	5 (0.4)	12 (0.5)	53 (1.3)

Source: Table 7.1.5.4.1 above
1 These System Organ Classes had no individual event terms which met criteria for inclusion in this table

In the above table, gastrointestinal events again occurred with higher frequency for liraglutide-treated patients, both when comparing to placebo and when comparing to active control.

The following table includes events which occurred at a frequency at least 1% higher in the pooled liraglutide group than in the pooled comparator group.

Table 7.1.5.4.4: Events Which Occurred at a Frequency at Least 1% Higher Among Patients in the Pooled Liraglutide Group than Among Patients in the Pooled Comparator Group

System Organ Class	Preferred Term	Pooled Comp N=2272 n (%)	Pooled LGT N=4211 n (%)
Any	Any	1437 (63.2)	3015 (71.6)
Gastrointestinal disorders	Any	455 (20.0)	1682 (39.9)
	Nausea	102 (4.5)	788 (18.7)
	Diarrhea	126 (5.5)	437 (10.4)
	Vomiting	45 (2.0)	285 (6.8)
	Constipation	57 (2.5)	234 (5.6)
	Dyspepsia	32 (1.4)	191 (4.5)
	Abdominal pain upper	27 (1.2)	94 (2.2)
Nervous system disorders	Any	371 (16.3)	786 (18.7)
	Dizziness	60 (2.6)	172 (4.1)
General disorders and administration site conditions	Any	195 (8.6)	514 (12.2)
	Fatigue	36 (1.6)	136 (3.2)
Metabolism and nutrition disorders	Any	156 (6.9)	483 (11.5)
	Decreased appetite	10 (0.4)	152 (3.6)
	Anorexia	15 (0.7)	137 (3.3)
Skin and subcutaneous tissue disorders[1]	Any	102 (4.5)	236 (5.6)

Source: Table 7.1.5.4.1 above
1 This System Organ Class had no individual event terms which met criteria for inclusion in this table

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When using this more specific presentation, gastrointestinal events, dizziness and fatigue occurred with an incidence at least 1% higher for liraglutide-treated patients than for comparator-treated patients.

Injection site reactions occurred more commonly among liraglutide-treated patients than among comparator-treated patients. In the five major Phase 3 trials of liraglutide, comparator-treated patients received injected comparator (either placebo or insulin glargine, depending on study). Therefore, comparisons of rates of injection site reactions are meaningful. The incidence of injection site reactions appeared to be dose-dependent among the proposed liraglutide doses. The applicant posits that this dose dependence is related to the increasing volume injected with increasing dose. However, this would not explain an imbalance in events of an inflammatory character (as opposed to events of bruising and pain, which might be related to dose volume). The following table displays the incidence of injection site events in the five major Phase 3 trials.

Table 7.1.5.4.5: Treatment-Emergent Injection Site Events, Five Major Phase 3 Trials

	Liraglutide 0.6 mg				Liraglutide 1.2 mg				Liraglutide 1.8 mg				Placebo				Active Comparator			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Safety Analysis Set	475				896				1130				524				953			
Total Exposure (yrs)	387.3				724.1				824.5				265.0				738.4			
Adverse Events																				
Total	7	(1.5)	7	18.1	16	(1.8)	20	27.6	27	(2.4)	31	37.6	8	(1.5)	9	34.0	11	(1.2)	11	14.9
General disorders and administration site conditions																				
Total	7	(1.5)	7	18.1	16	(1.8)	20	27.6	27	(2.4)	31	37.6	8	(1.5)	9	34.0	11	(1.2)	11	14.9
Injection Site Bruising	3	(0.6)	3	7.7	5	(0.6)	6	8.3	6	(0.5)	6	7.3	7	(1.2)	7	26.4	2	(0.2)	2	2.7
Injection Site Pain					3	(0.3)	3	4.1	6	(0.5)	6	7.3					3	(0.3)	3	4.1
Injection Site Irritation					1	(0.1)	1	1.4	4	(0.4)	4	4.9					2	(0.2)	2	2.7
Injection Site Pruritus									3	(0.3)	3	3.6					1	(0.1)	1	1.4
Injection Site Rash	2	(0.4)	2	5.2	3	(0.3)	3	4.1	3	(0.3)	3	3.6								
Injection Site Reaction					1	(0.1)	1	1.4	3	(0.3)	3	3.6								
Injection Site Erythema	2	(0.4)	2	5.2	1	(0.1)	1	1.4	2	(0.2)	2	2.4								
Injection Site Haemorrhage					2	(0.3)	2	2.8	2	(0.2)	2	2.4					1	(0.1)	1	1.4
Injection Site Mass					1	(0.1)	1	1.4	1	(0.1)	1	1.2								
Injection Site Nodule									1	(0.1)	1	1.2								
Injection Site Dermatitis					1	(0.1)	1	1.4					1	(0.2)	1	3.8				
Injection Site Discolouration																	1	(0.1)	1	1.4
Injection Site Discomfort													1	(0.2)	1	3.8				
Injection Site Haematoma					1	(0.1)	1	1.4												
Injection Site Hypersensitivity																	1	(0.1)	1	1.4

N: Number of Subjects with adverse events, %: Proportion of subjects in analysis set having adverse events
E: Number of adverse events, R: Number of events divided by Subject years of exposure multiplied by 1000
Total Exposure (yrs) : Total Exposure in years for Safety Analysis Set
For complete treatment regimens in the individual trials, see Table 1-1

Cross-reference: Appendix 7.2, Table 130

Source: Applicant's Table 2-59, pg 234, ISS

7.1.5.5 Identifying common and drug-related adverse events

Gastrointestinal events (particularly nausea, vomiting and diarrhea), injection site reactions, dizziness and fatigue are likely causally related to the use of liraglutide.

Numerical imbalances also exist for papillary thyroid cancer, C-cell hyperplasia events, pancreatitis, serious hypoglycemia events and overall malignancies. However, due to the low number of events for the former 4, and the relatively small imbalance for overall malignancies, causality cannot be definitively assigned. Imbalances in events potentially related to immunogenicity, and increases in heart rate, are discussed in Sections 7.1.10 and 7.1.8.3 below.

7.1.5.6 Additional analyses and explorations

See Section 7.4.2.

7.1.6 Less Common Adverse Events

After submission of the NDA, the applicant submitted a series of safety reports to IND 61040 of a case of "cryptogenic cirrhosis" from a patient treated with LGT 0.6 mg/day in Study NN2211-1796 in India. Patient 211018 was a 58 year old man who received LGT for 90 days before presenting with shortness of breath, black stools, and a hemoglobin of 6.2 g/dL. He had no history of alcohol consumption. He had esophageal varices on upper endoscopy, and banding was performed. Abdominal ultrasound revealed mild hepatomegaly with irregularities on the liver surface. Anti-smooth muscle antibody and antinuclear antibody results were negative. Liver biopsy was not performed. The final diagnosis was reported as "cryptogenic cirrhosis". The safety report did not include transaminase, bilirubin, alkaline phosphatase, hepatitis serology or coagulation values. Three days after presentation, study drug was discontinued. The patient reportedly recovered after 4 days of hospitalization. The report states that the patient resumed study medication 5 days after discharge, but then completed the study 16 days later. On 16 Jul 2009, the clinical safety reviewer requested that Novo provide all baseline and subsequent values for transaminases, bilirubin, alkaline phosphatase, coagulation studies, and any laboratory done to establish the etiology of the "cryptogenic cirrhosis". On 20 Jul 2009, the applicant submitted these data. At baseline and at Weeks 12 and 26, the patient had normal transaminase values. Bilirubin was elevated at baseline (1.09 mg/dL; ULN 0.25) and Week 26 (0.58 mg/dL). Coagulation studies and other studies regarding the etiology of cirrhosis were not available. The patient had mild thrombocytopenia at baseline ($99x10^9$/L, LLN $145x10^9$), but normal platelet counts during treatment. The etiology of the patient's varices is unclear, but it does not appear that he developed active liver dysfunction while taking liraglutide.

There was one other case of cirrhosis in the liraglutide development program (Patient 225011), but that patient appeared to have pre-existing disease and is discussed in Section 7.1.1.

Please see Section 7.1.3.2 for discussion of two patients who were withdrawn from study for mild transaminase elevations.

The following table displays all liver-related adverse events which occurred in the liraglutide development program. Transaminase and bilirubin laboratory evaluations are discussed in Section 7.1.7.3.

Table 7.1.6: Hepatic Adverse Events, All Completed Trials of Liraglutide as of 16 Jan 2009

	n (%)								
Preferred Term	**LGT <0.6**	**LGT 0.6**	**LGT >0.6-<1.2**	**LGT 1.2**	**LGT >1.2-<1.8**	**LGT 1.8**	**LGT >1.8**	**PBO**	**AC**
Hepatic steatosis		8 (1.2)		7 (0.7)		5 (0.4)	3 (1.0)	3 (0.3)	7 (0.6)
Hepatic calcification		1 (0.2)							1 (0.1)
Portal hypertension						1 (0.1)			
Liver disorder									1 (0.1)
Jaundice						1 (0.1)			
Hepatic cyst		1 (0.2)							
Hepatic cirrhosis				1 (0.1)					

Source: Applicant's Table 1-2, beg pg 98, NDA 22341 subm stamp date 16 Jan 2009

The event of jaundice was listed as a nonserious adverse event, and no narrative or patient identifier was provided. Further information has been requested for this patient. Overall, there were few hepatic adverse events, and the incidence among liraglutide-treated patients did not appear to be higher than that among comparator-treated patients.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

All clinical trials had measurements of standard hematology and chemistry parameters at baseline and end-of-study. The five major Phase 3 trials had additional measurements at intervals during the trial. Urinalysis was performed in the five major Phase 3 trials and in some intermediate-term trials. Calcitonin and thyroid blood tests were measured in some trials, and are discussed in Section 7.1.3.3.

Hematology parameters measured included basophils, eosinophils, lymphocytes, monocytes, neutrophils, total leukocytes, thrombocytes, hemoglobin and hematocrit.

Serum chemistry parameters measured included albumin, alanine aminotransferase, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatine phosphokinase, creatinine, potassium, aspartate aminotransferase, sodium, total calcium, free calcium, protein, uric acid and phosphorus.

Urinalysis parameters included albumin:creatinine ratio, glucose, hemoglobin, ketones, pH and protein.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The review focuses on laboratory findings from the five major Phase 3 trials. The applicant does present findings from shorter-term trials in their Integrated Summary of Safety, and findings are qualitatively similar.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

There were no significant differences between treatment groups over time for mean and median values of the hematology, serum chemistry and urinalysis parameters specified in Section 7.1.7.1.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There were no significant differences between treatment groups over time for the percentage of patients who had low or high values at a given time point, or who shifted from normal to high or low values, for the hematology parameters, and for most of the serum chemistry parameters specified in Section 7.1.7.1.

A slightly higher percentage of patients had serum total bilirubin levels that were above the upper limit of normal over time in the liraglutide groups than in the comparator groups.

Table 7.1.7.3.2: Percentage of Patients with Serum Total Bilirubin Levels Above the Upper Limit of Normal, Five Major Phase 3 Trials

Week[1]	LGT 0.6		LGT 1.2		LGT 1.8		PBO		AC	
	N[2]	%[3]	N[2]	%[3]	N[2]	%[3]	N[2]	%[3]	N[2]	%[3]
0	473	2.7	891	1.7	1123	1.9	521	1.1	947	2.4
12	431	2.3	774	1.8	962	1.6	419	1.0	849	1.2
26/28	466	3.6	864	1.0	1093	2.2	506	0.8	920	0.4
52	184	1.6	364	0.9	362	1.4	61	0	354	0.7
76/78	171	1.6	314	1.2	310	0.9	48	0	295	1.3

Source: Applicant's Table 210, pg 1521, ISS
1 Week 26/28 = Studies 1436, 1572, 1573, 1574 and 1697.
Week 52 = main trial for 1573 and extension for 1572.
Week 76/78 = extensions for 1572 and 1573.
2 N = # patients with at least one value
3 % = percentage of patients with value above the reference range at that time point

On 18 May 2009, the clinical safety reviewer requested that Novo provide the number and percentage of patients in each treatment group who had bilirubin elevations to >2x ULN, >3x ULN and >10x ULN. On 28 May 2009, the applicant reported that no patients had a bilirubin >2x ULN. However, this did not appear to be correct, because in Table 3-9 (pg 287 of integrated summary of safety [ISS]), patients are reported who had bilirubin elevations to 5x ULN (Pt 579006, LGT 1.8 mg, and Pt 761016, AC). Another query was sent to Novo on 14 Jul 2009 asking for an explanation for this discrepancy. On 17 Jul 2009, the applicant responded that the two patients identified by the clinical safety reviewer had been the only patients who had bilirubin elevations >2x ULN, and that these patients had not been identified by the applicant after the original query due to a programming error.

No patients fulfilled the criteria for Hy's law (individual patient with transaminase ≥3x ULN, bilirubin >ULN and normal alkaline phosphatase). There were also no individual patients who met criteria of a transaminase ≥3x ULN, bilirubin >ULN and alkaline phosphatase ≤2x ULN.

Dr. Parola, the Pharmacology/Toxicology reviewer, reports that monkeys which had significant injection site reactions also had peripheral eosinophilia. In data from the longterm trials of liraglutide, there did not appear to be a difference between liraglutide and comparator for the incidence of elevations in eosinophil levels or in shifts from normal to abnormal. However, automated hematology measurements might not be a sensitive measure of eosinophilia. In the Japanese study 1334, there was a dose-dependent increase in eosinophils, both in patients with DM2 and in obese subjects.

There was no difference between liraglutide and comparators for the percentage of patients who shifted from undetectable to detectable or ≥3+ protein on urinalysis.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

In most applications which the clinical safety reviewer has reviewed, the applicant has provided a table with laboratory values (high and/or low) which were defined as being potentially clinically significant. Such a table was not included in this NDA. Laboratory abnormalities were presented as "clinically significant" or "not clinically significant", but these terms were not defined. The Agency requested the definition of "clinically significant" for each laboratory parameter from the applicant. On 22 May, they responded:

"Upon receipt of a laboratory report, the investigator was required to asses (sic) the laboratory values being outside the normal range, evaluating clinical significance. Exact values defining clinical significance were not defined by the sponsor and the reporting of clinical significance was based on the investigators (sic) assessment of the patient's status and the normal ranges reported for these particular analyses."

In the clinical safety reviewer's opinion, this method of assigning "clinical significance" is potentially subjective, and could result in under-reporting of results that might have been considered clinically significant in other drug development programs that use a more structured

definition for outlier values. Therefore, specifically defined outlier results were requested for certain key laboratory parameters.

There were no significant differences between treatment groups over time for the percentage of patients who shifted from normal to "clinically significant" (as "defined" above) high or low values, for the hematology parameters specified in Section 7.1.7.1. This was also true for most serum chemistry parameters. For serum bilirubin, a slightly numerically higher percentage of liraglutide-treated patients shifted from normal to "clinically significant" high values, from baseline to 26 weeks. By 52 weeks, the number of patients who had exhibited such a shift was small in all treatment groups.

Table 7.1.7.3.3.1: Shifts from Baseline Normal to "Clinically Significant" High Values, Bilirubin

Time	LGT 0.6 n/N (%)	LGT 1.2 n/N (%)	LGT 1.8 n/N (%)	PBO n/N (%)	AC n/N (%)
BL-26/28 wks[1]	7/475 (1.5)	2/896 (0.2)	13/1130 (1.2)	2/524 (0.4)	2/953 (0.2)
BL-52 wks[2]	3/184 (1.6)	2/369 (0.5)	3/366 (0.8)	0	2/361 (0.6)

Source: Applicant's Table 186, beg pg 1470, ISS
1 All five major Phase 3 trials
2 Includes main portion of Study 1573 and open-label extension of Study 1572

The clinical safety reviewer requested information on all patients who had bilirubin values >2x ULN, as well as specified higher multiples. On 28 May 2009, the applicant reported that no values were >2x ULN, and all "clinically significant" values reported in the above table were >1x ULN but <2x ULN. However, this did not appear to be correct, because in Table 3-9 (pg 287 of ISS), patients are reported who had bilirubin elevations to 5x ULN (Pt 579006, LGT 1.8 mg, and Pt 761016, AC). Another query was sent to Novo on 14 Jul 2009 asking for an explanation for this discrepancy. On 17 Jul 2009, the applicant responded that the two patients identified by the clinical safety reviewer had been the only patients who had bilirubin elevations >2x ULN, and that these patients had not been identified by the applicant after the original query due to a programming error.

Patient 579006 was a 56 year old man who was treated with liraglutide 1.8 mg. He developed acute cholecystitis with elevated bilirubin, transaminases and alkaline phosphatase. The event appears to have resolved after 19 days.

In the 17 Jul 2009 submission, the applicant states that Patient 761006, a comparator-treated patient, had elevated bilirubin at baseline, and missing postbaseline values. No clinical history was given. In the Integrated Summary of Safety from the original NDA submission, it also appears that he had elevations of transaminases and alkaline phosphatase at some point during study, but there is no narrative.

The following table displays the number and percentage of patients who had transaminase values in specified ranges from the major Phase 3 trials. No patients had transaminase levels >10x ULN.

Table 7.1.7.3.3.2: Number and Percentage of Patients Who Had Transaminase Values In Specified Multiples of the Upper Limit of Normal, Five Major Phase 3 Trials

Lab	Range	LGT 0.6 N=475 n (%)	LGT 1.2 N=896 n (%)	LGT 1.8 N=1130 n (%)	PBO N=524 n (%)	AC N=953 n (%)
ALT (U/L)	>ULN	4 (0.8)	4 (0.4)	10 (0.9)	6 (1.1)	4 (0.4)
	>3x ULN	2 (0.4)	2 (0.2)	6 (0.5)	4 (0.8)	4 (0.4)
	>5x ULN	1 (0.2)		3 (0.3)	1 (0.2)	1 (0.1)
AST (U/L)	>ULN	5 (1.1)	4 (0.4)	10 (0.9)	6 (1.1)	4 (0.4)
	>3x ULN	4 (0.8)	2 (0.2)	8 (0.7)	3 (0.6)	2 (0.2)
	>5x ULN			2 (0.2)	1 (0.2)	

Source: Applicant's Table 3-9, pg 287, ISS
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

The number of patients who had transaminase elevations was small, and there was little difference between treatment groups.

On 17 Jul 2009, the applicant responded to a query regarding patients who had creatinine shifts to specified multiples of the upper limit of normal. In their response, it appeared that no patients had creatinine values that were >1.5x ULN. However, this did not appear to be correct, because in the Integrated Summary of Safety, the following findings were noted by the clinical safety reviewer:

- In Table 151 on page 1376, it appeared that there was at least one patient who had a creatinine of 4.65 mg/dL, which would be >2x ULN.
- Patient 389001 had an episode of renal tubular necrosis, and a creatinine of 3.7 mg/dL occurred, which would be >2x ULN.
- Patient 332023 had an event of acute renal failure with increased creatinine.
- Table 3-8 on page 284 indicated that there were 10 patients who had adverse events of blood creatinine increased.

On 21 Jul 2009, a request was made to the applicant to clarify these discrepancies.

There was no difference between liraglutide and comparators for the percentage of patients who developed ≥3+ protein on urinalysis.

7.1.7.4 Additional analyses and explorations

See Section 7.4.2.

7.1.7.5 Special assessments

Please see Section 7.1.3.3.2 for discussions of calcitonin measurements and thyroid ultrasound.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure and heart rate were measured in all clinical trials of liraglutide. Temperature and respiratory rate were measured in two small single-dose trials.

Blood pressure was an efficacy endpoint; see Dr. Yanoff's efficacy review for more extensive discussion of blood pressure findings in Phase 3 trials of liraglutide.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

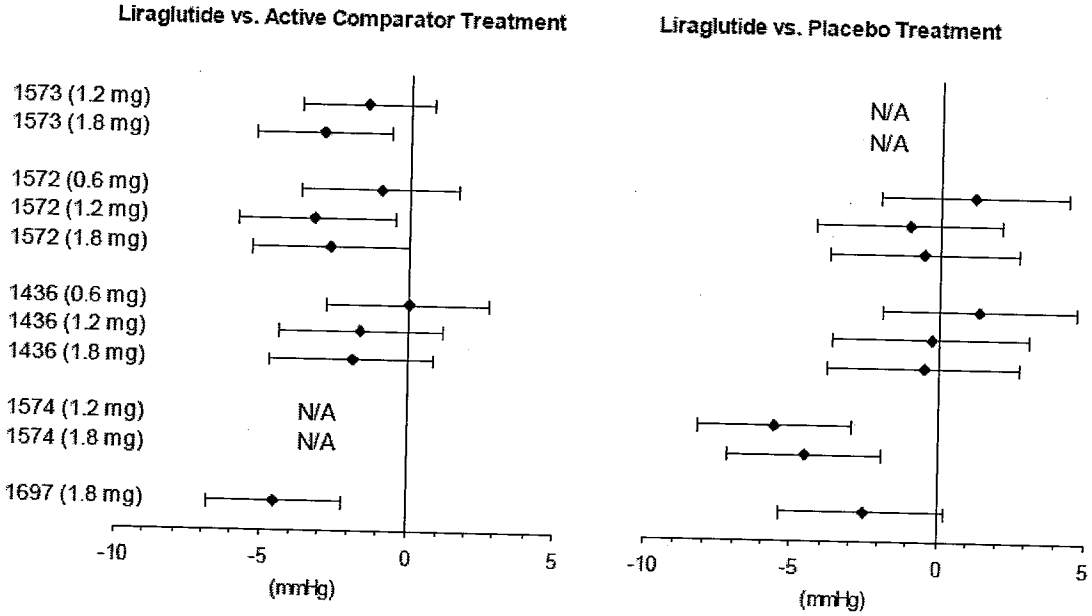
Data from the controlled, blinded portions of the five major Phase 3 trials were used for comparisons of vital signs data for blood pressure and pulse. Only single dose data were available for evaluation of temperature and respiratory rate.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

In the five major Phase 3 trials, liraglutide did not increase systolic blood pressure; most point estimates for liraglutide versus comparator favored liraglutide, particularly for comparisons to other active antidiabetic agents. The following figure displays point estimates and confidence intervals for change in systolic blood pressure.

Figure 7.1.8.3.1: Change from Baseline in Systolic Blood Pressure, Liraglutide versus Comparator, Five Major Phase 3 Trials



Source: Applicant's Figure 3-8, Summary of Clinical Efficacy, pg 117
Time period is from baseline to time of measurement of primary HbA1c efficacy endpoint

There was no significant effect of liraglutide on mean diastolic blood pressure in the Phase 3 trials.

Liraglutide was associated with a small but statistically significant increase in mean heart rate (2-3 beats per minute [bpm]) in the five major Phase 3 trials, as illustrated in the following repeated measurements analysis by the applicant.

Table 7.1.8.3.1: Repeated Measurements Analysis (by Novo) of Heart Rate (Beats per Minute), Five Major Phase 3 Trials

Comparison of levels in Pulse after 26/28, 52 and 76/78 weeks of treatment

Treatment / Comparison	Estimates			p-value
Week 26/28				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	1053	77.55	(0.31)	
Liraglutide 1.2mg	805	77.14	(0.34)	
Liraglutide 0.6mg	471	77.73	(0.40)	
Active Comparator	851	75.82	(0.31)	
Placebo	501	75.03	(0.41)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	1.73	[1.01 ;	2.45]	<.0001
Lira 1.2 vs. Active	1.32	[0.55 ;	2.09]	0.0009
Lira 0.6 vs. Active	1.91	[1.01 ;	2.82]	<.0001
Lira 1.8 vs. Placebo	2.52	[1.67 ;	3.37]	<.0001
Lira 1.2 vs. Placebo	2.11	[1.22 ;	3.00]	<.0001
Lira 0.6 vs. Placebo	2.70	[1.69 ;	3.72]	<.0001
Week 52				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	389	76.84	(0.41)	
Liraglutide 1.2mg	392	77.11	(0.41)	
Liraglutide 0.6mg	173	77.27	(0.57)	
Active Comparator	394	74.94	(0.40)	
Placebo	52	74.38	(0.98)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	1.90	[0.88 ;	2.91]	0.0002
Lira 1.2 vs. Active	2.17	[1.15 ;	3.19]	<.0001
Lira 0.6 vs. Active	2.33	[1.03 ;	3.63]	0.0004
Lira 1.8 vs. Placebo	2.46	[0.44 ;	4.47]	0.0167
Lira 1.2 vs. Placebo	2.73	[0.71 ;	4.75]	0.0080
Lira 0.6 vs. Placebo	2.89	[0.72 ;	5.05]	0.0089
Week 76/78				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	180	76.58	(0.54)	
Liraglutide 1.2mg	194	77.16	(0.53)	
Liraglutide 0.6mg	105	77.49	(0.70)	
Active Comparator	161	75.89	(0.57)	
Placebo	22	74.69	(1.44)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	0.69	[-0.77 ;	2.16]	0.3528
Lira 1.2 vs. Active	1.27	[-0.18 ;	2.72]	0.0851
Lira 0.6 vs. Active	1.61	[-0.10 ;	3.32]	0.0655
Lira 1.8 vs. Placebo	1.89	[-1.09 ;	4.86]	0.2135
Lira 1.2 vs. Placebo	2.46	[-0.50 ;	5.43]	0.1034
Lira 0.6 vs. Placebo	2.80	[-0.30 ;	5.90]	0.0766

The estimates are from an repeated measurement model with country, previous treatment, treatment, time, treatment by time as fixed effects and baseline pulse level as a covariate and subject as random effect
For complete treatment regimens in the individual trials, see Table 1-1

Cross-reference: Appendix 7.2, Table 243.

Source: Applicant's Table 4-1, Integrated Summary of Safety, pg 203

This increase in heart rate was associated with sinus rhythm in almost all cases. The occurrence of non-sinus dysrhythmias is displayed below in Table 7.1.8.3.3.

Limited single-dose data do not suggest a significant effect of liraglutide on body temperature or respiratory rate.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

See Section 7.1.8.3.3.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Two liraglutide-treated patients withdrew from study for increased heart rate, one from the 1.2 mg dose group in Study 1573, and one from the 1.8 mg dose group in Study 1572. No comparator-treated patients withdrew due to increased heart rate.

Adverse events related to heart rate occurred at a numerically higher frequency among liraglutide-treated patients than among comparator-treated patients. The following table displays adverse events related to heart rate.

Table 7.1.8.3.3: Adverse Events Related to Heart Rate, Five Major Phase 3 Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT 0.6 N=475 n (%)	LGT 1.2 N=896 n (%)	LGT 1.8 N=1130 n (%)	PBO N=524 n (%)	AC N=953 n (%)
Investigations	**Heart rate increased**	1 (0.2)	2 (0.2)	2 (0.2)	1 (0.2)	0
Cardiac disorders	**Tachycardia**	2 (0.4)	5 (0.6)	4 (0.4)	1 (0.2)	3 (0.3)
	Supraventricular tachycardia	0	1 (0.1)	2 (0.2)	0	0
	Ventricular tachycardia	0	0	1 (0.1)	1 (0.2)	0
	Sinus tachycardia	2 (0.4)	2 (0.2)	0	0	0
	Tachycardia paroxysmal	1 (0.2)	1 (0.1)	0	0	0

Source: Applicant's Table 4-3, pg 323, ISS

One liraglutide-treated patient withdrew due to increased blood pressure, from the 1.8 mg dose group in Study 1436. No comparator-treated patients withdrew due to blood pressure events.

7.1.8.4 Additional analyses and explorations

See Section 7.4.2.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were recorded at baseline and end-of-treatment in all trials of liraglutide, and at intermediate timepoints in some trials. A "thorough QT study" was also conducted.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Data from the controlled, blinded portions of the five major Phase 3 trials were used for evaluation of ECG data.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

There were no differences between liraglutide and comparator for mean changes in ECG intervals.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The number and percentage of patients who had a shift from normal to abnormal ECG findings was similar between liraglutide and comparator.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Outlier data for changes in ECG intervals were not presented for the longterm trials. However, outliers were evaluated in the thorough QT study, and no imbalance was noted. Additionally, PR, QT and QRS intervals were recorded in 3 single-dose trials (1149, 1464 and 1219) and in short-term trials 1189, and no significant changes occurred.

The following table displays adverse events related to ECG findings.

Table 7.1.9.3.3: Adverse Events Related to ECG Findings, All Completed Trials at Time of NDA Submission

Preferred Term	LGT N=4211 n (%)	PBO N=1122 n (%)	AC N=1165 n (%)
ECG signs of myocardial ischemia		1 (0.1)	
ECG abnormal	7 (0.2)	3 (0.3)	3 (0.3)
ECG QT prolonged	2 (<0.1)		
ECG change	1 (<0.1)		1 (0.1)
ECG T wave abnormal	1 (<0.1)		
ECG ST-T change		1 (0.1)	
ECG Q wave abnormal	1 (<0.1)		

Source: Applicant's Table 1-2, beg pg 9, NDA 22341 Submission Stamp Date 16 Jan 2009

Overall, there was not an imbalance in the percentage of patients with reported adverse events related to ECGs. Two events of QT prolongation occurred, but neither appeared clinically significant. One was reported in a Phase 2 study (1499) in a patient treated with liraglutide 1.8 mg. A narrative was not provided. The study report states that the patient had a normal baseline ECG, but at Week 6, had QT prolongation that was "not clinically significant". The actual QT interval was not reported. Subsequent ECGs were normal. Liraglutide was not discontinued. The second occurred in Study 1573 in a patient who had QT prolongation at screening, and who was treated with LGT 1.8 mg. On a subsequent ECG, QT prolongation was noted, but it was reportedly unchanged from baseline. The actual QT interval was not reported.

One liraglutide-treated patient discontinued study due to an event of "electrocardiogram abnormal". This appears to have been Patient 299003, who was a 42 year old man who received liraglutide 0.6 mg. After 242 days of treatment, he was noted to have "bifasic T-tap lateral" (sic) on ECG. He later underwent coronary angiography and "the examination showed that slight changes in ECG were not clinically relevant".

7.1.9.4 Additional analyses and explorations

The "thorough QT study" did not show evidence of risk for liraglutide-associated QT prolongation. Please see the review of this study by the Division of Cardiorenal Products (DFS 6 Jan 2009).

7.1.10 Immunogenicity

7.1.10.1 Antibody Formation

In the five main Phase 3 trials, antibodies to liraglutide were measured at Weeks 0, 12 and 26/27/28. In Trial 1573, they were also measured at Weeks 40 and 53.

Antibody data are presented for the pooled trials for Weeks 26/27/28, and for Week 53 for Trial 1573. Antibodies to liraglutide were measured 5 days after discontinuation of study drug, to minimize interference of circulating liraglutide with the assay.

The method of analysis was a radioimmunoprecipitation assay using [125I]-labeled liraglutide tracer and polyethylene glycol precipitation. The amount of precipitated radioactivity was measured and expressed as %B/T (percent bound radioactivity [B] of the total amount of radioactivity [T]). In the five major Phase 3 trials, subjects with antibody levels above 1.55% B/T were defined as positive for liraglutide antibodies. This value was chosen as an assay-specific cutpoint because it was the value associated with 5% false positive samples; this was intended to ensure detection of weakly positive samples. The method for defining antibody positivity is further explained on page 352 of the ISS. Antibody-positive samples were further analyzed for antibodies cross-reacting with native GLP-1, and for antibodies with a neutralizing effect on liraglutide in an *in vitro* cell-based assay.

Across the four major Phase 3 trials which measured their primary endpoint at 26 weeks, when considering only samples that were obtained ≥5 days off study drug, approximately 9-10% of liraglutide-treated patients were positive for anti-liraglutide antibodies, with little difference by liraglutide dose. Approximately 5-6% of liraglutide-treated patients had antibodies which cross-reacted with native GLP-1, with a slight inverse dose-response. Patients treated with placebo or active control did not develop anti-GLP-1 antibodies. Approximately 1-1.5% of liraglutide-treated patients developed antibodies which exhibited a neutralizing effect on liraglutide in the *in vitro* assay. At 52 weeks (and beyond), few patients had a sample obtained after ≥5 days off drug.

Table 7.1.10.1.1: Percentages of Patients with Liraglutide Antibodies at End of Treatment in the Four Major Phase 3 Trials Which Measured the Primary Endpoint at 26 Weeks (Measurement Off Drug ≥5 Days)

		LGT 0.6 N=475	LGT 1.2 N=896	LGT 1.8 N=1130	PBO N=524	AC N=953
End of Treatment (Completers)	# Pts with sample	215	342	547	291	422
	n (%)[1] with + LGT Ab	21 (9.8)	32 (9.4)	49 (9.0)	1 (0.3)	1 (0.2)
	n (%)[1] with anti-LGT neutralizing effect	3 (1.4)	4 (1.2)	5 (0.9)	0	0
	n (%)[1] with cross-reactivity to native GLP-1	13 (6.0)	18 (5.3)	25 (4.6)	0	0
End of Treatment (LOCF)	# Pts with sample	229	388	603	316	448
	n (%)[1] with + LGT Ab	21 (9.2)	32 (8.2)	49 (8.1)	1 (0.3)	1 (0.2)
	n (%)[1] with anti-LGT neutralizing effect	3 (1.3)	4 (1.0)	5 (0.8)	0	0
	n (%)[1] with cross-reactivity to native GLP-1	13 (5.7)	18 (4.6)	25 (4.1)	0	0

Source: Applicant's Table 248, pg 1578, ISS
Trials 1436, 1572, 1574, 1697
1 Percentage of patients who had a sample

In these same four trials, maximum % B/T for anti-liraglutide antibody was 10.7%, in a patient treated with LGT 1.2 mg/day. The following table displays measures of central tendency of patients who were positive for anti-liraglutide antibodies, by treatment group.

Table 7.1.10.1.2: Summary of Measures of Central Tendency for Patients Who Had Positive Anti-Liraglutide Antibodies (% B/T); Studies 1436, 1572, 1574 and 1697

		LGT 0.6 n[1]=21	LGT 1.2 n[1]=32	LGT 1.8 n[1]=49	PBO n[1]=1	AC n[1]=1
End of Treatment (Completers)	Mean (SD)	3.3 (1.5)	2.9 (1.9)	3.5 (2.0)	2.8 (n/a)	1.6 (n/a)
	Median	2.9	2.3	2.7	2.8	1.6
	Min;Max	1.6;7.7	1.6;10.7	1.6;9.0	2.8;2.8	1.6;1.6
End of Treatment (LOCF)	Mean (SD)	3.3 (1.5)	2.9 (1.9)	3.5 (2.0)	2.8 (n/a)	1.6 (n/a)
	Median	2.9	2.3	2.7	2.8	1.6
	Min;Max	1.6;7.7	1.6;10.7	1.6;9.0	2.8;2.8	1.6;1.6

Source: Applicant's Table 251, pg 1582, ISS
1 n = # of patients who had a + anti-LGT antibody measurement

Novo presented several methods of assessing for clinical correlates of antibody formation.

Among these was a comparison of the types of adverse events which occurred among those patients who developed anti-liraglutide antibodies, and those who did not. For those who

developed antibodies, the most frequent SOC for adverse events was "Infections and Infestations", while for those who did not develop antibodies, the most common SOC was "Gastrointestinal Disorders". For the SOC of "Infections and Infestations", the differences between antibody-positive and non-antibody-positive were accounted for by small numerical differences in the incidence of several infections, primarily of the nasopharynx and upper respiratory system, as presented in the following table.

Table 7.1.10.1.3: Events from the System Organ Class "Infections and Infestations" Which Occurred With Higher Frequency Among Patients Positive for Anti-Liraglutide Antibodies than Among Patients Negative for Anti-Liraglutide Antibodies, Five Major Phase 3 Trials at Time of NDA Submission

Preferred Term	LGT Ab+ N=160 n (%)	LGT Ab- N=2341 n (%)	PBO Ab- N=521 n (%)	AC Ab- N=945 n (%)
Any infection or infestation Preferred Term	64 (40.0)	837 (35.8)	177 (34.0)	333 (35.2)
Upper respiratory tract infection	18 (11.3)	154 (6.6)	34 (6.5)	48 (5.1)
Gastroenteritis	6 (3.8)	66 (2.8)	7 (1.3)	20 (2.1)
Urinary tract infection	6 (3.8)	75 (3.2)	9 (1.7)	21 (2.2)
Pharyngitis	5 (3.1)	31 (1.3)	9 (1.7)	14 (1.5)
Lower respiratory tract infection	4 (2.5)	5 (0.2)	2 (0.4)	9 (1.0)
Cystitis	3 (1.9)	9 (0.4)	1 (0.2)	7 (0.7)
Gastroenteritis viral	3 (1.9)	28 (1.2)	2 (0.4)	9 (1.0)

Source: Applicant's Tables 309 and 311, beginning on pages 2757 and 2803 of ISS

In addition to events in the above SOC, the following events occurred in at least 3 liraglutide-treated patients who were antibody-positive, and occurred with higher numerical frequency than among patients who were antibody-negative.

Table 7.1.10.1.4: Events from the System Organ Classes other than "Infections and Infestations", Which Occurred With Higher Frequency Among Patients Positive for Anti-Liraglutide Antibodies than Among Patients Negative for Anti-Liraglutide Antibodies, Five Major Phase 3 Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT=Ab+ N=160 n (%)	LGT=Ab- N=2341 n (%)	PBO=Ab- N=521 n (%)	AC=Ab- N=945 n (%)
Gastrointestinal disorders	Any	59 (36.9)	1008 (43.1)	93 (17.9)	175 (18.5)
	Dyspepsia	10 (6.3)	112 (4.8)	7 (1.3)	19 (2.0)
	Abdominal discomfort	5 (3.1)	26 (1.1)	3 (0.6)	4 (0.4)
	Abdominal pain upper	5 (3.1)	58 (2.5)	5 (1.0)	12 (1.3)
	Toothache	5 (3.1)	39 (1.7)	8 (1.5)	18 (1.9)
	Gingivitis	3 (1.9)	5 (0.2)	0	2 (0.2)
Musculoskeletal and connective tissue	Any	33 (20.6)	367 (15.7)	68 (13.1)	164 (17.4)

Table 7.1.10.1.4: Events from the System Organ Classes other than "Infections and Infestations", Which Occurred With Higher Frequency Among Patients Positive for Anti-Liraglutide Antibodies than Among Patients Negative for Anti-Liraglutide Antibodies, Five Major Phase 3 Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT=Ab+ N=160 n (%)	LGT=Ab- N=2341 n (%)	PBO=Ab- N=521 n (%)	AC=Ab- N=945 n (%)
disorders					
	Back pain	12 (7.5)	99 (4.2)	14 (2.7)	43 (4.6)
	Arthralgia	7 (4.4)	38 (1.6)	9 (1.7)	40 (4.2)
	Myalgia	5 (3.1)	43 (1.8)	6 (1.2)	20 (2.1)
	Neck pain	3 (1.9)	14 (0.6)	2 (0.4)	9 (1.0)
General disorders and administration site conditions	Any	23 (14.4)	273 (11.7)	46 (8.8)	83 (8.8)
Nervous system disorders	Any	23 (14.4)	423 (18.1)	65 (12.5)	150 (15.9)
	Headache	17 (10.6)	224 (9.6)	39 (7.5)	80 (8.5)
	Dizziness	7 (4.4)	85 (3.6)	12 (2.3)	21 (2.2)
	Hypoaesthesia	3 (1.9)	17 (0.7)	1 (0.2)	6 (0.6)
Metabolism and nutrition disorders	Any	18 (11.3)	307 (13.1)	38 (7.3)	70 (7.4)
	Dyslipidemia	6 (3.8)	31 (1.3)	11 (2.1)	12 (1.3)
Respiratory, thoracic and mediastinal disorders	Any	14 (8.8)	165 (7.0)	36 (6.9)	66 (7.0)
	Rhinitis allergic	3 (1.9)	8 (0.3)	0	4 (0.4)
Skin and subcutaneous tissue disorders	Any	12 (7.5)	151 (6.5)	24 (4.6)	45 (4.8)
	Rash	4 (2.5)	26 (1.1)	5 (1.0)	12 (1.3)
	Pruritus	3 (1.9)	17 (0.7)	2 (0.4)	3 (0.3)
Cardiac disorders	Any	8 (5.0)	104 (4.4)	17 (3.3)	30 (3.2)
	Angina pectoris	3 (1.9)	14 (0.6)	3 (0.6)	2 (0.2)
Eye disorders	Any	8 (5.0)	132 (5.6)	27 (5.2)	51 (5.4)
	Diabetic retinopathy	5 (3.1)	32 (1.4)	7 (1.3)	16 (1.7)
Blood and lymphatic system disorders	Any	6 (3.8)	37 (1.6)	7 (1.3)	11 (1.2)
	Anemia	4 (2.5)	21 (0.9)	6 (1.2)	6 (0.6)
Ear and labyrinth disorders	Any	5 (3.1)	39 (1.7)	5 (1.0)	15 (1.6)
Immune system disorders	Any	4 (2.5)	30 (1.3)	0	8 (0.8)

Source: Applicant's Tables 309 and 311, beginning on pages 2757 and 2803 of ISS

In general, the pattern of events in the above table does not suggest a significant clinical correlate of adverse events which occur significantly more frequently among antibody-positive patients compared to antibody-negative patients (other than the aforementioned infection events). Musculoskeletal pain may have occurred more commonly among antibody-positive patients. The imbalance in events from the SOC "General Disorders and Administration Site Conditions" may have been due to a slightly higher numerical rate of certain injection site reactions among

antibody-positive patients. This was difficult to discern, however, because of the small total number of antibody-positive patients. There were also several types of injection site adverse event terms which were reported for some antibody-negative patients that were not reported for antibody-positive patients. The following table lists all injection site events which occurred, for antibody-positive liraglutide-treated patients, and for antibody-negative patients.

Table 7.1.10.1.5: Injection Site Events Among Antibody-Positive Liraglutide-Treated Patients, and Among Antibody-Negative Patients, Five Major Phase 3 Trials at Time of NDA Submission

Preferred Term	LGT Ab+ N=160 n (%)	LGT Ab- N=2341 n (%)	PBO Ab- N=521 n (%)	AC Ab- N=945 n (%)
Injection site erythema	2 (1.3)	3 (0.1)	0	0
Injection site pain	2 (1.3)	7 (0.3)	0	3 (0.3)
Injection site pruritus	2 (1.3)	1 (<0.1)	0	1 (0.1)
Injection site rash	2 (1.3)	6 (0.3)	0	0
Injection site irritation	1 (0.6)	4 (0.2)	0	2 (0.2)
Injection site reaction	1 (0.6)	3 (0.1)	0	0
Injection site bruising	0	14 (0.6)	7 (1.3)	2 (0.2)
Injection site hemorrhage	0	4 (0.2)	0	1 (0.1)
Injection site mass	0	2 (0.1)	0	0
Injection site nodule	0	1 (<0.1)	0	0
Injection site dermatitis	0	1 (<0.1)	1 (0.2)	0
Injection site discoloration	0	0	0	1 (0.1)
Injection site discomfort	0	0	1 (0.2)	0
Injection site hematoma	0	1 (<0.1)	0	0
Injection site hypersensitivity	0	0	0	1 (0.1)

Source: Applicant's Tables 309 and 311, beginning on pages 2757 and 2803 of ISS

Dr. Parola, the Pharmacology/Toxicology reviewer, reports that monkeys which had significant injection site reactions also had peripheral eosinophilia. In data from the longterm trials of liraglutide, there did not appear to be a difference between liraglutide and comparator for the incidence of elevations in eosinophil levels or in shifts from normal to abnormal. However, automated hematology measurements might not be a sensitive measure of eosinophilia. In the Japanese study 1334, there was a liraglutide-associated dose-dependent increase in eosinophils, both in patients with DM2 and in obese subjects (Source ISS, Table 3-3, pg 276 and Table 3-7, pg 281).

The applicant performed searches of potential immunogenicity events using 3 Standard MedDRA Queries. The following table lists terms included in these SMQs.

Table 7.1.10.1.6: Terms Included in Standard MedDRA Queries for Immunogenicity Events

MedDRA SMQ	Preferred Terms		
Anaphylactic reaction	Anaphylactic reaction	Anaphylactoid shock	Type I hypersensitivity
	Anaphylactic shock	Circulatory collapse	
	Anaphylactoid reaction	Shock	
Angioedema	Allergic oedema	Hereditary angioedema	Small bowel angioedema
	Angioedema	Idiopathic urticaria	Swelling face
	Circumoral oedema	Laryngeal oedema	Swollen tongue
	Conjunctival oedema	Laryngotracheal oedema	Tongue oedema
	Corneal oedema	Lip oedema	Tracheal oedema
	Epiglottic oedema	Lip swelling	Urticaria
	Eye oedema	Oculorespiratory syndrome	Urticaria cholinergic
	Eye swelling	Oedema mouth	Urticaria chronic
	Eyelid oedema	Oropharyngeal swelling	Urticaria papular
	Face oedema	Palatal oedema	
	Gingival oedema	Periorbital oedema	
	Gingival swelling	Pharyngeal oedema	
	Gleich's syndrome	Scleral oedema	
Severe cutaneous reactions	Acute generalised exanthematous pustulosis.	Dermatitis exfoliative generalised.	Skin necrosis
	Cutaneous vasculitis	Epidermal necrosis	Stevens-Johnson syndrome
	Dermatitis bullous	Erythema multiforme	Toxic epidermal necrolysis
	Dermatitis exfoliative	Exfoliative rash	Toxic skin eruption

Source: Applicant's Table 2-53, pg 227, ISS

No patients who were antibody-positive had events which fell under these SMQs. However, as shown in Table 7.1.10.2.1, liraglutide-treated patients overall did have a higher numerical frequency of events from these SMQs than did comparator-treated patients.

The applicant also explored for evidence of an effect of antibody formation on efficacy. In the four Phase 3 trials which measured the primary endpoint at 26 weeks (1436, 1572, 1574 and 1697), Novo performed an analysis for an interaction by Ab+ status on HbA1c at 26 weeks. There did not appear to be a treatment interaction by presence of anti-liraglutide antibodies in general, or by presence of cross-reactivity of the antibody with native GLP-1. There was a trend, albeit not statistically significant, of an interaction by the presence of liraglutide-neutralizing antibodies, as shown in Table 7.1.10.1.7 below. However, there were few samples with + neutralizing effect, and the trend was for slightly greater reduction in HbA1c, rather than for less reduction in HbA1c, as shown in Table 7.1.10.1.8 below.

Table 7.1.10.1.7: Analysis of Treatment Effect by Positive Liraglutide Antibody Interaction on HbA1c (%), Pooled Liraglutide Groups, Studies 1436, 1572, 1574 and 1697)

Type of Antibody Positivity	Antibody Presence Status	N[1]	Factor Effect p-value	Treatment by Factor Interaction[2] p-value
Positive liraglutide Ab	Absent	1073	0.2899	0.6810
	Present	101		
Positive liraglutide-neutralizing effect *in vitro*	Absent	1073	0.1522	0.7751
	Present	12		
Positive cross-reacting effect with native GLP-1	Absent	1073	0.8009	0.9067
	Present	56		

Source: Applicant's Table 5-3, pg 174, Summary of Clinical Efficacy
1 Applicant defines N as the number of subjects with data available for this analysis
2 Applicant states that the p-value of treatment by factor interaction was calculated by ANCOVA model: change in HbA1c = baseline HbA1c + treatment + country + previous antidiabetic drug + factor + treatment * factor interaction + trial + trial * treatment

Table 7.1.10.1.8: Summary of Change in HbA1c by Treatment and Neutralizing Antibody Positivity; Baseline to Week 26; Patients Who Had an Antibody Measurement ≥5 Days off Study Drug; Studies 1572, 1436, 1574 and 1697

Treatment[1]		Neutralizing Antibody Status	
		Absent	Present
LGT 0.6	N	202	3
	Mean Change HbA1c (SD)	-0.5 (1.0)	-1.4 (0.6)
LGT 1.2	N	337	4
	Mean Change HbA1c (SD)	-1.2 (1.1)	-1.6 (1.7)
LGT 1.8	N	534	5
	Mean Change HbA1c (SD)	-1.2 (1.1)	-1.6 (0.7)

Source: Applicant's Table 5-4, pg 175, Summary of Clinical Efficacy
1 No patients in placebo or active control groups had neutralizing antibodies .

The following table lists all patients with the highest antibody titres (%B/T >5) and their change in HbA1c from baseline to measurement of the primary endpoint.

Table 7.1.10.1.9: Change in HbA1c from Baseline to Measurement of Primary Endpoint, Patients with Anti-Liraglutide Antibody %B/T >5, All Completed Trials at Time of NDA Submission

ID	LGT Dose (mg)	LGT Ab (%B/T)	X-Reacting Effect[1] (%B/T)	Neutr?	Δ HbA1c (%)
579026	1.2	10.7	0	-	0
180020	1.2	9.9	8.8	-	-0.1
606008	1.8	9.0	1.7	-	-0.2
778008	1.8	8.3	7.0	-	-0.9
587010	0.6	7.7	2.8	-	-0.7
809010	1.8	7.6	7.8	-	-0.8
587021	1.8	7.5	9.5	-	-0.5
717005	1.8	7.2	3.2	-	-0.7
571023	1.2	7.0	2.4	-	-1.1
580018	1.8	6.3	1.5	-	-0.7

Table 7.1.10.1.9: Change in HbA1c from Baseline to Measurement of Primary Endpoint, Patients with Anti-Liraglutide Antibody %B/T >5, All Completed Trials at Time of NDA Submission

ID	LGT Dose (mg)	LGT Ab (%B/T)	X-Reacting Effect[1] (%B/T)	Neutr?	Δ HbA1c (%)
332030	1.8	6.1	2.2	+	-2.0
762011	1.8	5.9	7.3	-	-3.5
675001	1.8	5.8	4.4	-	-0.6
529017	1.2	5.7	3.1	-	-2.1
808011	1.8	5.6	1.5	-	-1.1
528008	0.6	5.5	0	-	-0.8
675002	1.8	5.5	2.5	-	-1.7

Source: Applicant's Listing 26, beg pg 3858, ISS
1 Cross-reaction with native GLP-1

The three patients with the highest %B/T values (≥9%) had little change from baseline to endpoint in HbA1c (Δ HbA1c 0 to -0.2), while patients with lower antibody titres had HbA1c changes that were typical of the mean changes in the clinical trials, or higher in a few cases. The lack of decline in HbA1c for the 3 patients with the highest titres did not appear to be associated with high cross-reactivity with native GLP-1, or with anti-liraglutide neutralizing effect. These three cases are too few to reach conclusions, but it is possible that patients who develop higher titres of anti-liraglutide antibodies may have some diminution in efficacy.

7.1.10.2 Other Explorations for Immunogenicity

The applicant performed Standard MedDRA Query searches for immunogenicity events. Events from these queries did occur numerically more frequently among liraglutide-treated patients than among comparator-treated patients (LGT 0.6% of pts versus comp 0.2%, rate 11.6 versus 4.4 events per 1000 patient-years). All events were classified as nonserious except one case of angioedema (Patient 375005). Two other patients were withdrawn from study due to events of lip swelling (Patient 259007) and urticaria (356011). The following table lists the events which occurred from the immunogenicity SMQs.

Table 7.1.10.2.1: Events from MedDRA Standard Queries Related to Immunogenicity, All Completed Trials at Time of NDA Submission

SMQ	Preferred Term	LGT N=4211 n (%)	COMP N=2272 n (%)
Any Immunogenicity SMQ	**Any**	24 (0.6)	5 (0.2)
Angioedema	**Any**	22 (0.5)	3 (0.1)
	Urticaria	11 (0.3)	2 (0.1)
	Angioedema	2 (<0.1)	0
	Pharyngeal edema	2 (<0.1)	0
	Eye edema	1 (<0.1)	0
	Eyelid edema	1 (<0.1)	1 (<0.1)
	Face edema	1 (<0.1)	0
	Lip swelling	1 (<0.1)	0

Table 7.1.10.2.1: Events from MedDRA Standard Queries Related to Immunogenicity, All Completed Trials at Time of NDA Submission

SMQ	Preferred Term	LGT N=4211 n (%)	COMP N=2272 n (%)
	Edema mouth	1 (<0.1)	0
	Periorbital edema	1 (<0.1)	0
Anaphylactic reaction	Any	1 (<0.1)	1 (<0.1)
	Anaphylactic reaction	1 (<0.1)	0
	Circulatory collapse	0	1 (<0.1)
Severe cutaneous reactions	Any	1 (<0.1)	1 (<0.1)
	Dermatitis bullous	1 (<0.1)	1 (<0.1)

Source: Applicant's Table 2-57, pg 230, ISS

The applicant states that adverse events of immunogenicity were dose-related. However, this relationship is not entirely clear, as illustrated in the following table.

Table 7.1.10.2.2: Incidence and Rates (per 1000 Patient-Years) of Treatment-Emergent Adverse Immunogenicity Events by Liraglutide Dose, All Completed Trials at Time of NDA Submission

	LGT Dose (mg)						
	<0.6 N=377 PY=64	0.6 N=641 PY=418	>0.6 and <1.2 N=417 PY=39	1.2 N=993 PY=758	>1.2 and <1.8 N=73 PY=12	1.8 N=1408 PY=870	>1.8 N=302 PY=82
SAEs Rate/ 1000 PY	0	0	0	1.3	0	0	0
Nonserious AEs Rate/ 1000 PY	0	4.8	25.6	14.5	0	10.3	24.5
Total AEs Rate/ 1000 PY	0	4.8	25.6	15.8	0	10.3	24.5
SAEs n (%)	0	0	0	1 (0.1)	0	0	0
Nonserious AEs n (%)	0	2 (0.3)	1 (0.2)	9 (0.9)	0	9 (0.6)	2 (0.7)
Total AEs n (%)	0	2 (0.3)	1 (0.2)	10 (1.0)	0	9 (0.6)	2 (0.7)

Source: Applicant's Table 122, beg pg 1316, ISS

Brief narratives of immunogenicity events follow.

Patient 375005 was a 60 year old woman who had an event of angioedema. The event occurred after 211 days of liraglutide, 1.2 mg/day. Shortly after receiving an Bioparox (fusafungine) for acute laryngopharyngitis, the patient developed difficulty in swallowing, lid and facial swelling, and a sensation of suffocation. She was hospitalized and treated with intravenous glucocorticoids. She recovered and was discharged 9 days later. Liraglutide was not discontinued.

Patient 415004 was a 53 year old man who had a nonserious event with the Preferred Term angioedema, with an investigator term of giant urticaria. Because this was a nonserious event, no narrative was provided. He had received liraglutide 1.8 mg for 102 days at the time of the event; it resolved after two days. Liraglutide was not discontinued.

Patient 259007 was a 44 year old man who had an event of lower lip swelling after 7 days of treatment with liraglutide, 1.8 mg. He recovered the next day and was not hospitalized, but was withdrawn from study.

Patient 356011 was a 49 year old man who developed urticaria after 5 days of treatment with liraglutide (dose not specified). The next day, nausea and vomiting also occurred. The patient was not hospitalized and recovered 2 days later, but was withdrawn from study.

Patient 505001 was a 53 year old woman who had two episodes of "anaphylaxis reaction". One episode occurred after 146 days of liraglutide (dose not specified), and one occurred after 255 days. The second episode had a descriptor of "wheal", but no further information was provided in the narrative. Liraglutide was not discontinued.

Patient 2606 was a 54 year old man who had a nonserious event of pharyngeal edema, which occurred after 83 days of treatment with liraglutide (dose not specified). The event severity was listed as mild and there was no narrative. The event was reported on the patient's last planned day of study participation.

Patient 333001 was a 60 year old woman who had a nonserious event of pharyngeal edema (investigator term "shollen [sic] throat") after 1 day of liraglutide. The event severity was listed as mild and there was no narrative. The event resolved after 5 days and liraglutide was not discontinued.

Patient 9555 was a 69 year old man who had a nonserious event of "dermatitis bullous" with an investigator term of "rupture blister inside lower hip [sic]". He had received liraglutide (dose not specified) for 84 days. No narrative was provided and liraglutide was not discontinued.

All other events from Table 7.1.10.2.1 were nonserious, did not have narratives, and did not result in discontinuation of study drug.

Please see Section 7.1.3.2 for a discussion of two patients who discontinued liraglutide treatment due to events of hypersensitivity.

Please also see Table 7.1.2.2 and accompanying discussion regarding overall immune system adverse events. There did not appear to be a liraglutide-associated increase in the rate of these events.

7.1.11 Human Carcinogenicity

Please see Section 7.1.3.3.2 for a discussion of thyroid cancer. Overall malignancies are discussed in Section 7.1.11.

As shown in Table 7.1.11 below, there was a numerical imbalance, not favoring liraglutide, in the percentage (0.5% versus 0.3%) of patients who were reported to have serious adverse events from the System Organ Class "Neoplasms, Benign, Malignant and Unspecified", and an imbalance in the rate per 1000 patient years (8.9 versus 5.3) of events from this SOC.

Table 7.1.11.1: Serious Events from the System Organ Class "Neoplasms, Benign, Malignant and Unspecified", All Completed Trials at Time of NDA Submission

	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
Serious Neoplasm Event	**n**	**%**	**Rate per 1000 PY**	**n**	**%**	**Rate per 1000 PY**
Any	19	0.5	8.9	6	0.3	5.3
Papillary thyroid cancer	4	0.1	1.8	1	<0.1	0.9
Prostate cancer	4	0.1	1.8	1	<0.1	0.9
Breast cancer	2	<0.1	0.9	1	<0.1	0.9
B-cell lymphoma	1	<0.1	0.4	0	0	0
Benign neoplasm of thyroid gland	1	<0.1	0.4	0	0	0
Colon adenoma	1	<0.1	0.4	0	0	0
Gastrointestinal carcinoma	1	<0.1	0.4	0	0	0
Hepatic neoplasm malignant	1	<0.1	0.4	0	0	0
Lung carcinoma cell type unspecified recurrent	1	<0.1	0.4	0	0	0
Malignant lymphoma unclassifiable high grade	1	<0.1	0.4	0	0	0
Nasopharyngeal cancer	1	<0.1	0.4	0	0	0
Renal cell carcinoma stage unspecified	1	<0.1	0.4	1	<0.1	0.9
Uterine leiomyoma	1	<0.1	0.4	0	0	0
Colon cancer	0	0	0	1	<0.1	0.9
Glioblastoma multiforme	0	0	0	1	<0.1	0.9

Source: Applicant's Table 72, beg pg 1123, ISS

When one removes the three patients who had benign neoplasms, the percentages of patients with serious malignant neoplasms are 0.4% for liraglutide-treated patients and 0.3% for non-liraglutide-treated patients, and the rates are 7.1 events per 1000 PY for liraglutide-treated patients and 5.3 events per 1000 PY for non-liraglutide-treated patients. When one also removes the patients with papillary thyroid cancer, the percentages become 0.3% versus 0.2%, and the rates become 5.4 versus 4.9 events per 1000 PY, respectively.

In the safety update, serious malignant neoplasm events were reported for an additional 7 liraglutide-treated patients and 1 comparator-treated patient. The events in liraglutide-treated patients were breast cancer, colon cancer (3 patients), papillary thyroid cancer, adenocarcinoma pancreas and "metastases to liver". The event in a comparator-treated patient was "metastatic neoplasm". The updated rates of serious adverse events of neoplasm were 12.3 and 8.1 events per 1000 patients years for LGT and comparator, respectively. When one considers only malignant neoplastic events, the updated totals of patients with events were 26 for LGT and 10

for comparator (10.7 versus 8.1 events per 1000 patient-years). Removal of the papillary cancer event changed the rate ratio to 10.3 versus 8.1 events per 1000 PY.

These numerical imbalances are not statistically significant. However, given recent concerns regarding a possible epidemiologic link between insulin(s) and cancer, the imbalance is of concern, as liraglutide causes an increase in insulin levels. The non-thyroid malignancies which occurred among liraglutide-treated patients were of cell types that are potentially life-threatening, and the imbalance is not accounted for by an excess of non-life-threatening malignancies (such as non-melanoma skin cancers).

The following table displays the duration of exposure prior to diagnosis of the serious adverse events of malignant neoplasms.

Table 7.1.11.2: Duration of Exposure Prior to Diagnosis of Serious Adverse Events of Malignant Neoplasms, All Completed Trials at Time of NDA Submission

Pt ID	Malignancy	Tx	LGT Exp (Days)
16004	Papillary thyroid cancer	LGT 0.6	99
506001	Papillary thyroid cancer	LGT 1.8	175
261006	Papillary thyroid cancer	LGT 1.2	356
326016	Papillary thyroid cancer	LGT 1.8	50
500005	Prostate cancer	LGT 1.8	156
342004	Prostate cancer	LGT 0.6	340
128005	Prostate cancer	LGT 1.2	539
175022	Prostate cancer	LGT 1.8	417
156002	Breast cancer	LGT 1.2	28
158012	Breast cancer	LGT 1.8	214
709005	B-cell lymphoma	LGT 1.2	228
266008	Gastrointestinal carcinoma	LGT 1.2	143
225011	Hepatic neoplasm malignant	LGT 1.2	182
122004	Lung carcinoma type unspecified recurrent	LGT 1.8	156
300003	Malignant lymphoma unclassifiable high grade	LGT 0.6	142
256004	Nasopharyngeal cancer	LGT 1.8	442
28001	Renal cell carcinoma stage unspecified	LGT 0.9	56
326008	Papillary thyroid cancer	Comp	61
736002	Prostate cancer	Comp	171
504034	Breast cancer	Comp	315
386003	Renal cell carcinoma stage unspecified	Comp	353
200002	Colon cancer	Comp	586
707009	Glioblastoma multiforme	Comp	195

Source: Serious adverse event narratives, beg pg 3930, ISS

Agents that increase cancer risk may be either initiators or promoters. In general, for nongenotoxic agents, exposure of short duration is considered less likely to be consistent with causality of initiation of a malignancy. Agents with genotoxicity may initiate malignancy after shorter exposure, but may still be associated with a latent period prior to appearance of the malignancy. The potential genetic toxicity of liraglutide has not been fully characterized, as discussed in Section 3.2. Agents which are promoters may cause more rapid growth of underlying malignancies, which may not have been evident at the time of initiation of treatment. In the liraglutide development program, limited information is available for long durations of

exposure; at the time of submission of the NDA (and at the time of the safety update), 840 patients had been exposed for >50 weeks.

In the above table, one patient who was treated with liraglutide was diagnosed with breast cancer 28 days after initiation of therapy; it is unlikely that this malignancy was causally related to liraglutide. For the remainder of liraglutide-treated cases, 2 occurred at <3 months of therapy; 6 occurred at >3-6 months; 6 occurred at >6-12 months; and 2 occurred at >12 months. Among comparator-treated patients, numbers of cases for these time periods were 1, 1, 3 and 1, respectively.

The following table displays the number and percentage of patients who had any event of neoplasm (serious or nonserious), for all completed trials at the time of NDA submission.

Table 7.1.11.3: Number and Percentage of Patients with Any Neoplasm Event (Serious or Nonserious), All Completed Trials at Time of NDA Submission

Preferred Term	LGT N=4211 n (%)	Non-LGT N=2272 n (%)
Any neoplasm term	53 (1.3)	12 (0.5)
Thyroid neoplasm	15 (0.4)	4 (0.2)
Prostate cancer	4 (0.1)	1 (<0.1)
Papillary thyroid cancer	4 (0.1)	1 (<0.1)
Uterine leiomyoma	2 (<0.1)	1 (<0.1)
Melanocytic nevus	2 (<0.1)	1 (<0.1)
Lung neoplasm	3 (0.1)	
Lipoma	3 (0.1)	
Breast cancer	2 (<0.1)	1 (<0.1)
Skin papilloma	2 (<0.1)	
Renal cell carcinoma stage unspecified	1 (<0.1)	1 (<0.1)
Benign breast neoplasm	2 (<0.1)	
Basal cell carcinoma	2 (<0.1)	
Squamous cell carcinoma	1 (<0.1)	
Parathyroid tumor benign	1 (<0.1)	
Neuroma	1 (<0.1)	
Neoplasm skin	1 (<0.1)	
Nasopharyngeal cancer	1 (<0.1)	
Morton's neuroma	1 (<0.1)	
Malignant lymphoma unclassifiable high grade	1 (<0.1)	
Lung carcinoma cell type unspecified recurrent	1 (<0.1)	
Hepatic neoplasm malignant	1 (<0.1)	
Glioblastoma multiforme		1 (<0.1)
Gastrointestinal carcinoma	1 (<0.1)	
Colon cancer		1 (<0.1)
Colon adenoma	1 (<0.1)	
Benign neoplasm of thyroid gland	1 (<0.1)	
Benign neoplasm of skin	1 (<0.1)	
B-cell lymphoma	1 (<0.1)	

Source: Applicant's Table 1-2, beg pg 9, NDA 22341 subm stamp date 16 Jan 2009

Overall, 1.3% of liraglutide-treated patients had any event of neoplasm, while 0.5% of comparator-treated patients did so. The number of events in this table is greater than the number of patients who had any event, indicating that some patients had more than one event. Therefore, one cannot subtract out papillary thyroid cancer event terms to determine the remaining percentage of patients who had any event other than papillary thyroid cancer. However, it appears that removal of papillary thyroid cancer events would lessen, but not eliminate, the imbalance between treatment groups for the overall incidence of neoplasms. Otherwise, the neoplasms seen among liraglutide-treated patients were spread among different cell types. Time-to-event data were not presented for patients with nonserious events of neoplasms.

7.1.12 Special Safety Studies

See Section 7.1.9.4 regarding the "thorough QT study".

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Examination of pooled data from the five major Phase 3 trials for patients who had been off study drug for at least 7 days did not reveal a difference in post-treatment adverse events profiles between liraglutide and comparator.

Liraglutide would not be expected to cause psychological dependence. There is the potential for off-label use for weight loss. Off-label use of drugs for the purpose of weight loss is sometimes associated with features of drug abuse, such as drug-seeking behavior and continuation of the drug despite undesirable adverse effects.

7.1.14 Human Reproduction and Pregnancy Data

As of the time of the 120-day safety update, 8 pregnancies had occurred in the liraglutide development program. The following table provides information regarding those pregnancies and their outcomes.

Table 7.1.14: Pregnancies and Outcomes as of 120-Day Safety Update (Cut-Off 30 May 2008)

ID	Age (y)	Tx	Duration of Tx Prior to Pregnancy Diagnosis (days)	Pregnancy Outcome
173052	36	LGT 3.0	414	Induced termination "due to social circumstances"
118017	40	LGT 1.8	50	Healthy baby
571012	40	LGT 1.2	7	Elective abortion
389008	28	LGT 1.8	196	Healthy baby
131	19	LGT 1.8	11	Miscarriage
364022	41	MET	218	Miscarriage
617016	38	RSG + GLIM	189	Miscarriage
172031	34	PBO	0	Lost to follow-up

Source: Applicant's Table 5-1, pg 128, Safety Update, stamp date 23 Sep 2008

Few pregnancies occurred, and meaningful conclusions regarding the effect of liraglutide exposure during pregnancy cannot be reached. However, 2/3 liraglutide-treated patients who did not terminate their pregnancies had healthy babies.

Based on the occurrence of major fetal anomalies in the offspring of mice and rabbits who were exposed to less than the expected human clinical exposure, Dr. Parola, the Pharmacology/Toxicology reviewer, recommends Pregnancy Category C for liraglutide. The clinical safety reviewer concurs.

It is not known whether liraglutide is excreted in human milk. In lactating rats, liraglutide was excreted unchanged in milk at levels approximately 50% of those in rat maternal plasma.

7.1.15 Assessment of Effect on Growth

Liraglutide has not been studied in children or adolescents.

7.1.16 Overdose Experience

One patient (579008), a 65 year old man, accidentally administered a single dose of 17.4 mg, rather than the prescribed 0.6 mg. He presented with a history of 10-15 episodes of sweating, vomiting and abdominal discomfort. He was admitted to the hospital. Vital signs and ECG were normal. He had "memory disturbances" with regard to names and calculations. The narrative does not mention whether amylase or lipase were measured. He was treated with ondansetron, ranitidine, 10% intravenous dextrose, and saline. He recovered and was discharged after 3 days.

7.1.17 Postmarketing Experience

As of 1 Jun 2009, liraglutide is not approved in any country.

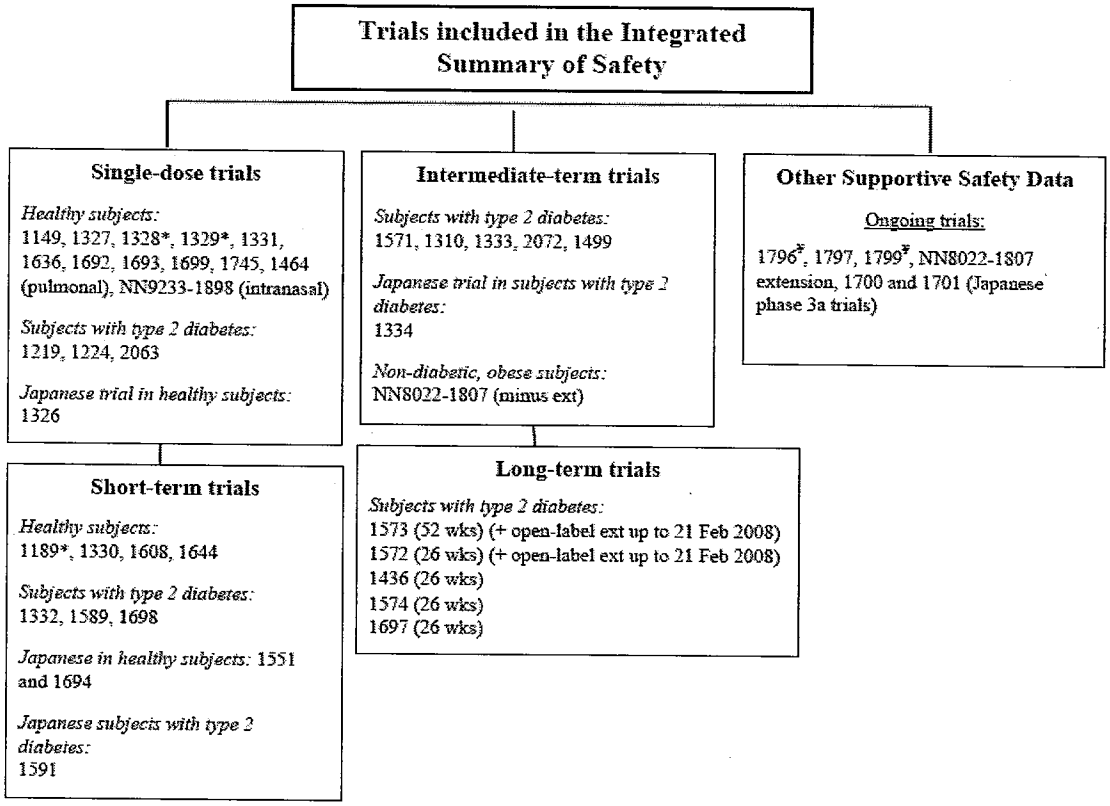
7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

In the original NDA, the applicant submitted data from 38 completed clinical trials. One trial (NN8022-1807) was a Phase 2 dose-finding trial for the treatment of obesity in nondiabetic subjects. Two Phase 1 trials explored alternate routes of administration; intranasal in NN9233-1898 and pulmonary in NN2211-1464. The other trials were conducted in healthy volunteers or patients with diabetes for the diabetes indication. Seven trials were conducted exclusively in Japanese subjects. At the time of NDA submission, there were also six ongoing trials. The applicant grouped the trials by duration, as illustrated in the following figure:

Figure 7.2.1.1



Total: 38 trials + 2 open-label extensions, 6 ongoing trials
*included 5, 3 and 4 subjects with type 2 diabetes, respectively
* did not contribute subject exposure in this document

Source: Applicant's Figure 1-1, pg 23, ISS

7.2.1.2 Demographics

The following table displays demographics and some baseline characteristics of the five major Phase 3 trials.

Table 7.2.1.2.1: Demographic and Baseline Characteristics, Major Phase 3 Trials

Characteristic	Category	Study 1436 N=1041	Study 1572 N=1091	Study 1573 N=746	Study 1574 N=533	Study 1697 N=581
Age	Mean yrs ± SD	56.1 ± 9.8	56.8 ± 9.5	53.0 ± 10.9	55.1 ± 10.2	57.5 ± 9.9
Gender	% male	49.4	58.2	49.7	55.9	56.5
Race[1]	% Caucasian	64.4	87.1	77.5	82.7	75.0
	% Black	2.8	2.4	12.6	11.8	3.6
	% Asian/Pacific Islander	32.4	9.0			15.7
	% Native Hawaiian/Pacific Islander			0.3		
	% Asian			3.5	1.9	
	% American Indian/ Alaska Native				0.8	
	% Unknown					4.8
	% Other	0.5	1.6	6.2	2.8	0.9
Ethnicity[1]	% Hispanic/Latino			35.0	15.2	
Diabetes duration	Mean yrs ± SD	7.9 ± 5.4	7.4 ± 5.2	5.4 ± 5.3	9.0 ± 5.6	9.4 ± 6.2
Previous diabetes treatment	Only diet and exercise (%)			36.5		
	Monotherapy (%)	30.3	35.3	63.5	16.9	5.7
	Combination therapy (%)	69.7	64.7		83.1	94.3
Weight	Mean kg ± SD	81.6 ± 17.4	88.6 ± 17.3	92.6 ± 19.6	97.0 ± 18.9	85.4 ± 18.3
Body Mass Index	Mean kg/m^2 ± SD	29.9 ± 5.1	31.0 ± 4.7	33.1 ± 5.8	33.5 ± 5.2	30.5 ± 5.3

Source: Table 6, beg pg 28, Statistical Review, Dr. Derr, DFS 20 May 2009
1 Race and ethnicity were categorized differently between trials. Trials which were conducted in the U.S. included a category for Hispanic ethnicity

Baseline characteristics were examined by treatment arm for each trial, and were generally well-matched.

All intermediate and longterm trials had an exclusion criterion for patients with significant cardiovascular disease, and thus a high incidence of cardiovascular events would not be expected among the population studied in the development program. There were also exclusion criteria for elevated baseline creatinine (generally max 1.3 mg/dL for women, 1.5 for men), which would eliminate a high cardiovascular risk group. Detailed recording of specific baseline cardiovascular risk characteristics had not been preplanned for the trials. In general, it was not a high-risk population. Some elements of baseline cardiovascular risk which could be assessed

included reports of prior MI (3.4%), baseline hypertension (66.8%), baseline term "hyperlipidemia" (23.3%), baseline term "hypercholesterolemia" (15.2%), and baseline term "dyslipidemia" (16.0%). Examination of data from the Phase 3 trials did not reveal any marked imbalances in the incidence of baseline cardiovascular conditions or baseline concomitant cardiovascular medication use between liraglutide groups and comparator groups (Sources: Study 1436 report, Table 14.1.8, beg pg 230; Study 1572 report, Table 14.1.8, beg pg 263; Study 1573, Table 14.1-8, beg pg 186; Study 1574, Table 14.1-8, beg pg 167; Study 1697, Table 14.1.8, beg pg 209; Integrated Summary of Safety Table 1-21, beg pg 72).

The following table displays the baseline incidence of complications of diabetes in Studies 1572, 1436 and 1697.

Table 7.2.1.2.2: Number and Percentage of Patients with Baseline Complications of Diabetes in Trials 1436, 1572 and 1697

	Liraglutide Arms			Placebo Control	Active Control	Total
Trial 1436 (26 weeks; add-on to glimepiride 4 mg)	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**rosiglitazone 4 mg**	**Total**
Retinopathy	40 (17.2)	34 (14.9)	28 (12.0)	15 (13.2)	38 (16.4)	155 (14.9)
Neuropathy	53 (22.7)	39 (17.1)	45 (19.2)	19 (16.7)	52 (22.4)	208 (20.0)
Nephropathy	21 (9.0)	9 (3.9)	11 (4.7)	2 (1.8)	12 (5.2)	55 (5.3)
Macroangiopathy[1]	19 (8.2)	23 (10.1)	23 (9.8)	6 (5.3)	27 (11.6)	98 (9.4)
Trial 1572 (26 weeks; add-on to metformin 2 g)	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**glimepiride 4 mg**	**Total**
Retinopathy	32 (13.2)	39 (16.2)	30 (12.4)	19 (14.8)	25 (10.2)	144 (13.2)
Neuropathy	48 (19.8)	38 (15.8)	44 (18.2)	22 (18.0)	38 (15.6)	190 (17.4)
Nephropathy	10 (4.1)	19 (7.9)	17 (7.0)	8 (6.6)	16 (6.6)	70 (6.4)
Macroangiopathy[1]	37 (15.3)	26 (10.8)	23 (9.5)	10 (8.2)	31 (12.7)	127 (11.6)
Trial 1697 (26 weeks; add-on to glimepiride 4 mg + metformin 2 g)			**liraglutide 1.8 mg +**	**placebo**	**insulin glargine**	**Total**
Retinopathy			46 (19.8)	27 (23.5)	48 (20.5)	121 (20.8)
Neuropathy			51 (22.0)	20 (17.4)	51 (21.8)	122 (21.0)
Nephropathy			17 (7.3)	7 (6.1)	16 (6.8)	40 (6.9)
Macroangiopathy[1]			31 (13.4)	16 (13.9)	37 (15.8)	84 (14.5)

Sources: Study 1436 report, Table 11-4, pg 96; Study 1572 report, Table 11-3, pg 104; Study 1697 report, Table 11-4, pg 95
1 Macroangiopathy included peripheral vascular disease

Definitions for retinopathy, neuropathy, nephropathy and macroangiopathy were not provided in the application. The Division requested the definitions, and on 13 Feb 2009, the applicant responded that there had not been specific definitions. At screening, concomitant illness was recorded on the case report form, which specifically included sections for the above complications of diabetes. The applicant stated that "A specific diagnostic definition for the specific complications was not given and the recording was based on the investigator's assessment." Although 6.1% of patients were reported to have baseline nephropathy, recall that a baseline creatinine above 1.3 for women, and above 1.5 for men, was an exclusion criterion. Therefore, these were generally not patients with advanced renal disease.

Across the development program, withdrawals due to adverse events were more common among LGT-treated patients than among comparator-treated patients. This excess withdrawal rate was due largely to gastrointestinal events, and was seen primarily for the 1.2 and 1.8 mg/day dose groups. The most common reason for withdrawal from the 0.6 mg/day dose group was ineffectiveness of therapy. Withdrawals due to ineffectiveness of therapy were more common among placebo-treated patients than among liraglutide or active comparator group patients.

Please see Tables 7.1.3.1.1 and 7.1.3.1.2 for information regarding disposition in the five major Phase 3 trials.

7.2.1.3 Extent of exposure (dose/duration)

At the time of NDA submission, across all trials, 4211 subjects had been exposed to liraglutide. Of these, 2086 had been exposed for at least 24 weeks, and 840 had been exposed for at least 50 weeks. At the time of submission of the 120-day safety update (23 Sep 2008), 4655 subjects had been exposed to liraglutide. Of these, 2412 had been exposed for at least 24 weeks, and the number of patients exposed for >50 weeks remained at 840.

The following table displays the number of patients exposed by treatment arm, study population and trial duration. The applicant has listed trials specifically required by Japanese regulatory authorities separately.

Table 7.2.1.3.1: Liraglutide Exposure by Treatment Arm, Study Population and Trial Duration, All Completed Trials at Time of NDA Submission

Trial Duration	Study Population	LGT N	PBO N	Active Comp N
Single dose	**Healthy subjects**	288	23	24
	DM2	47	40	
	Healthy Japanese subjects	24	8	
Short-term (1-7 wks)	**Healthy subjects**	164	155	
	DM2	63	61	31
	Healthy Japanese subjects	36	12	
	Japanese DM2	11	4	
Intermediate-term (8-20 wks)[1]	**DM2**	526	151	62
	Japanese DM2	180	46	
	Obese, non-DM2	371	98	95
Longterm (≥ 26 wks)	**DM2**	2501	524	953
Total	**All**	**4211**	**1122**	**1165**

Source: Applicant's Table 1-2, pg 31, ISS, Module 5.3.5.3
1 In intermediate trials, Applicant included Study 1499, which was a 5-week trial
Abbreviations: Comp = comparator, DM2 = type 2 diabetes mellitus, LGT = liraglutide, PBO = placebo, wks = weeks

The following table displays liraglutide exposure by duration of exposure.

Table 7.2.1.3.2: Liraglutide Exposure by Duration of Exposure, All Completed Trials at Time of NDA Submission

Trial Duration	Study Population	1 Day	>1 Day	≥5 Wks	≥12 Wks	≥24 Wks	≥50 Wks	≥76 Wks
Single dose	Healthy subjects	141	147					
	DM2	47						
	Healthy Japanese subjects	24						
Short-term (1-7 wks)	Healthy subjects	2	162	14				
	DM2	1	62	1				
	Healthy Japanese subjects		36	18				
	Japanese DM2		11					
Intermediate-term (8-20 wks)[1]	DM2		526	475	333			
	Japanese DM2		180	177	174			
	Obese, non-DM2	2	369	349	329	1		
Longterm (≥ 26 wks)	DM2	7	2494	2339	2222	2085	840	497
Total Subjects	**All**	**224**	**3987**	**3373**	**3058**	**2086**	**840**	**497**
Total Subject-Years	**All**	**1**	**2241**	**2214**	**2166**	**1865**	**1226**	**784**

Source: Applicant's Table 1-3, pg 34, ISS, Module 5.3.5.3
1 In intermediate trials, Applicant included Study 1499, which was a 5-week trial
Abbreviations: DM2 = type 2 diabetes mellitus, LGT = liraglutide, PBO = placebo, Wks = weeks

The following table displays liraglutide exposure by dose.

Table 7.2.1.3.3: Liraglutide Exposure by Dose, All Completed Trials at Time of NDA Submission

Trial Duration	Study Population	SQ Daily Dose in Mg n (%)[1]							IV n (%)[1]	INH n (%)[1]
		<0.6	0.6	>0.6 - <1.2	1.2	>1.2 - <1.8	1.8	>1.8		
Single dose	Healthy subjects	48 (9.7)	30 (3.7)	192 (39.5)		12 (9.7)			6 (100)	39 (100)
	DM2	17 (3.4)	1 (0.1)	29 (6.0)						
	Healthy Japanese subjects	12 (2.4)	3 (0.4)	9 (1.9)						
Short-term (1-7 wks)	Healthy subjects	14 (2.8)	144 (18.0)	6 (1.2)	142 (12.3)		140 (9.9)			
	DM2	12 (2.4)	18 (2.2)	3 (0.6)	18 (1.6)		48 (3.4)			
	Healthy Japanese subjects	36 (7.3)	1 (0.1)	26 (5.3)		9 (7.3)		1 (0.3)		
	Japanese DM2	11 (2.2)		4 (0.8)						
Intermediate-term (8-20 wks)[2]	DM2	253 (51.2)	85 (10.6)	173 (35.6)		103 (83.1)		101 (35.1)		
	Japanese DM2	91 (18.4)	45 (5.6)	44 (9.1)						
	Obese, non-DM2				95 (8.3)		90 (6.4)	186 (64.6)		
Longterm (≥ 26 wks)	DM2		475 (59.2)		896 (77.8)		1130 (80.3)			
Total Subjects	**All**	**494 (100)**	**802 (100)**	**486 (100)**	**1151 (100)**	**124 (100)**	**1408 (100)**	**288 (100)**	**6 (100)**	**39 (100)**

Source: Applicant's Table 1-4, pg 35, ISS
1: % of all patients exposed to this dose; each column should add up to 100%
2 In intermediate trials, Applicant included Study 1499, which was a 5-week trial
Abbreviations: DM2 = type 2 diabetes mellitus, INH = inhaled, IV = intravenous, SQ = subcutaneous

Across the development program, the greatest number of patients exposed to liraglutide was at the 1.8 mg dose, which is the highest dose proposed by the applicant.

Please see Table 7.2.9.7 for exposure at the time of the Safety Update.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

To the clinical safety reviewer's knowledge, no completed studies of liraglutide have been performed that were not submitted by the applicant to the NDA.

7.2.2.2 Postmarketing experience

As of 1 Jun 2009, liraglutide had not been approved in any country.

7.2.2.3 Literature

A literature review was performed; articles are cited through the review in individual sections.

7.2.3 Adequacy of Overall Clinical Experience

In general, data were adequate to assess the liraglutide-associated risk for most adverse events. However, the duration of the studies in the clinical trial program was not of sufficient duration for one to be able to expect to capture cases of medullary thyroid cancer. This cancer is often indolent in terms of rate of growth, and in the animal carcinogenicity studies, there was a long latency period from first exposure to appearance of C-cell adenomas and carcinomas.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see Dr. Parola's Pharmacology/Toxicology review. Additional studies may be needed to further clarify the human relevance of the rodent C-cell tumor findings. Also, genetic toxicity of impurities may not have been fully assessed. Local skin and subcutaneous reaction risk may not have been fully evaluated, because the concentration of the agent used in the animal studies was $1/10^{th}$ that of the proposed clinical formulation.

7.2.5 Adequacy of Routine Clinical Testing

See Section 7.2.3.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Dr. Khurana felt that the Clinical Pharmacology data were adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Please see Section 9.1. Data were inadequate to assess the human risk for medullary thyroid carcinoma, and to fully assess the risk for major adverse cardiovascular events.

7.2.8 Assessment of Quality and Completeness of Data

In general, other than the deficiencies cited for data regarding risks of medullary thyroid cancer and major adverse cardiovascular events, and some problems with laboratory data discussed below, data were complete at the time of NDA submission and permitted adequate review. The applicant provided additional data when requested.

During the review cycle, there were some issues with data quality regarding laboratory reporting for serum calcitonin, bilirubin and creatinine. There was a discrepancy regarding missing calcitonin values, which the applicant attributed to programming errors. Two sets of errata were submitted. During the review of bilirubin and creatinine data, the clinical safety reviewer noted that the applicant's analyses had omitted some patients who had elevated values. The applicant attributed the bilirubin data omissions to a programming error, and submitted errata. A response from the applicant regarding the creatinine elevation reporting discrepancy is pending.

7.2.9 Additional Submissions, Including Safety Update

After the original NDA submission, the applicant sent in 41 subsequent submissions to the NDA (as of 17 Jul 2009).

7.2.9.1 ECG Raw Datasets (18 Jun 2008)

These datasets were requested by the Division of Cardiorenal Drug Products, and were used in the review of the "thorough QT study", which found no significant QT prolongation effect of liraglutide, 1.8 mg (DFS 6 Jan 2009).

7.2.9.2 Historical Control Data for Mouse and Rat Carcinogenicity Studies (8 Jul 2008)

Dr. Parola, the Pharmacology Toxicology reviewer, requested this submission and used it in his review of the carcinogenicity study (DFS 15 Sep 2008).

7.2.9.3 Response to Request for Additional Data on Thyroid Neoplasms (11 Jul 2008)

Prior to submission of the NDA, the clinical reviewer for the [redacted] for liraglutide requested data regarding thyroid neoplasms across the obesity and diabetes development programs. Most of these data are presented in Section 7.1.3.3.2 above. Some additional data are summarized below.

b(4)

A table was requested of all adverse events potentially related to thyroid neoplasms (benign or malignant). The following table summarizes that information. The malignant neoplasms, and several of the benign neoplasms, are discussed in Section 7.1.3.3.2 above.

Table 7.2.9.3.1: Summary of All Thyroid Neoplasms (Benign and Malignant) Across the Obesity and Diabetes Drug Development Programs, as of 11 Jul 2008 Submission

Study	Pt ID	Age (years) and Gender	Tx	Preferred Term	Time from Rand to Detection	BL C-tonin (ng/L)	Pk C-tonin (ng/L) and Time
1334	5011	65 m	LGT 0.1	Thyroid neoplasm	99 d	3.2	4.8 (Wk 10)
1334	6017	59 f	LGT 0.1	Thyroid neoplasm	96 d	<1	26 (Wk 12)
1334	14007	72 m	LGT 0.1	Thyroid neoplasm	100 d	<1	48 (Wk 14)
1334	16004	70 f	LGT 0.6	Papillary thyroid cancer	99 d	<1	1.8 (Wk 2)
1334	20005	58 f	LGT 0.6	Thyroid neoplasm	100 d	24	39 (Wk 10)
1334	22001	58 m	LGT 0.6	Thyroid neoplasm	100 d	2.1	3.5 (Wk 6)
1334	26006	61 f	LGT 0.1	Thyroid neoplasm	99 d	27	37 (Wk 12)
1334	29001	54 m	LGT 0.3	Thyroid neoplasm	98 d	2.3	3.8 (Wk 4)
1334	31001	48 m	LGT 0.1	Thyroid neoplasm	99 d	3.2	54 (Wk 14)
1334	59006	70 f	LGT 0.1	Thyroid neoplasm	29 d	<1	21 (Wk 2)
1334	63002	57 m	LGT 0.1	Thyroid neoplasm (2 events)	71 and 97 d	5.2	48 (Wk 8)
1436	506001	59 m	LGT 1.8	Papillary thyroid cancer	175 d	13	23 (Wk 12)
1436	598016	64 f	LGT 1.2	Thyroid neoplasm	99 d	<0.7	<0.7 (BL)
1573	139003	78 m	LGT 1.2	Thyroid neoplasm	7 d	7.6	7.6 (BL)
1573	261006	62 f	LGT 1.2	Papillary thyroid cancer	356 d	1.7	4.6 (Wk 64)
1574	316010	54 f	LGT 1.2	Thyroid neoplasm	109 d	<0.7	<0.7 (BL)
1574	326016	53 f	LGT 1.8	Papillary thyroid cancer	50 d	10.7	10.7 (BL)
1700	47002	72 m	LGT 0.9	Thyroid neoplasm	288 d	<2	<2 (BL)
1797	476001	57 f	LGT 1.8	Thyroid neoplasm	45 d	<0.7	<0.7 (BL)
1334	12006	63 f	PBO	Thyroid neoplasm	97 d	1.2	1.2 (BL)

Table 7.2.9.3.1: Summary of All Thyroid Neoplasms (Benign and Malignant) Across the Obesity and Diabetes Drug Development Programs, as of 11 Jul 2008 Submission

Study	Pt ID	Age (years) and Gender	Tx	Preferred Term	Time from Rand to Detection	BL C-tonin (ng/L)	Pk C-tonin (ng/L) and Time
1334	26005	72 f	PBO	Thyroid neoplasm	99 d	<1	22 (Wk 12)
1573	136003	55 m	GLIM	Thyroid neoplasm	365 d	2.5	3.7 (Wk 52)
1574	326008	59 m	MET + RSG	Papillary thyroid cancer	61 d[1]	19.4	19.4 (BL)

Source: Applicant's Table 1 (beg serial pg 40) and Table 2 (serial pg 46), NDA 22341 submission stamp date 11 Jul 2008
1 The applicant's table states that the exposure was 1 day, but the clinical safety reviewer calculates 61 days.

At the time of this submission, there were 19 events of thyroid neoplasms among 4211 liraglutide-treated patients (0.5% of pts with event), and 4 events among 2287 comparator-treated patients (0.2% of pts with event).

Please see Section 7.1.3.3.2.5 for a discussion of Study 1334, a study performed in Japan which included routine thyroid ultrasound examinations. In this study, one liraglutide-treated patient had a reported event of papillary thyroid cancer. All other events were reported under the Preferred Term "thyroid neoplasm", and most of these were reported in brief narratives to have been thyroid nodules detected on ultrasound.

The submission also provided the number and percentage of patients who had serum calcitonins >ULN, >2x ULN, >3x ULN, etc. The following table summarizes those data for the main (non-extension) portions of the five major Phase 3 trials from the original NDA submission.

Table 7.2.9.3.2: Number and Percentage of Patients with Unstimulated Calcitonin Elevations in Specified Multiples of the Upper Limit of Normal, Main Portions of the Five Major Phase Trials from the Original NDA Submission

Week	Calcitonin Elevation Range	All LGT N=2501 n (%)	All Comp N=1477 n (%)
12	>ULN	135 (6.4)	61 (5.0)
	>2x ULN	26 (1.2)	12 (1.0)
	>3x ULN	6 (0.3)	5 (0.4)
	>5x ULN	1 (<0.1)	1 (0.1)
26 (completers)	>ULN	150 (7.3)	60 (5.2)
	>2x ULN	30 (1.5)	12 (1.0)
	>3x ULN	6 (0.3)	1 (0.1)
	>5x ULN	2 (0.1)	0

Source: Applicant's Table 6, serial pg 111, NDA 22341 submission stamp date 11 Jul 2008

At 12 and 26 weeks, there was a numerical imbalance in the percentage of patients with calcitonin elevations of any degree, and of elevations >2x ULN, not favoring liraglutide.

The following table includes only those patients who had normal renal function at baseline, using the Cockcroft-Gault equation.

Table 7.2.9.3.3: Number and Percentage of Patients with Normal Baseline Renal Function, and with Unstimulated Calcitonin Elevations in Specified Multiples of the Upper Limit of Normal, Main Portions of the Five Major Phase 3 Trials from the Original NDA Submission

Week	Calcitonin Elevation Range	All LGT N=1819 n (%)	All Comp N=1101 n (%)
12	>ULN	99 (6.3)	50 (5.4)
	>2x ULN	15 (1.0)	10 (1.1)
	>3x ULN	4 (0.3)	3 (0.3)
	>5x ULN	1 (0.1)	1 (0.1)
26 (completers)	>ULN	112 (7.3)	48 (5.6)
	>2x ULN	21 (1.4)	8 (0.9)
	>3x ULN	5 (0.3)	1 (0.1)
	>5x ULN	2 (0.1)	0

Source: Applicant's Table 8, serial pg 115, NDA 22341 submission stamp date 11 Jul 2008

At Week 12, when considering only patients with normal renal function at baseline, there was little difference between liraglutide and comparator for the percentage of patients who had calcitonin values in the specified ranges of multiples of normal. At Week 26, there was a numerical imbalance, not favoring liraglutide, for each of the specified ranges.

7.2.9.4 Submission of Raw Data Listings for Study 1572 (14 Aug 2008)

The raw data listings for Study 1572 in the original NDA submission had not contained listings for all patients, and these additional listings were included in this submission. Data from these listings was incorporated into the relevant sections of the review.

7.2.9.5 Response to 74-Day Filing Letter (25 Aug 2008)

This was a response to requests in the 74-Day Filing Letter from the Chemistry, Manufacturing and Controls Reviewer.

7.2.9.6 First Set of Analyses of Major Cardiovascular Events (17 Sep 2008)

This submission included analyses of MACE for which the applicant defined the endpoints and chose the analysis methods. See Section 7.1.3.3.1 for a discussion of results.

7.2.9.7 Safety Update (23 Sep 2008)

The safety update included some additional extension data, preliminary results from a trial of liraglutide versus exenatide, additional MACE analyses, and a preliminary Risk Management Plan.

Please see Section 7.1.3.3.1 for a discussion of the MACE analyses. The Risk Management Plan has subsequently been replaced by an updated version as part of a proposed Risk Evaluation and Mitigation Strategy (REMS). This REMS was submitted on 8 Jul 2009 (See Section 7.2.9.40 below).

The original NDA had included data from the controlled blinded portions of completed trials out to 31 Jan 2008, and for the open-label extension periods of Studies 1572 and 1573 out to 21 Feb 2008. The safety update included data from completed and ongoing trials out to 30 May 2008.

At the time of the safety update, 4655 patients had been exposed to liraglutide, 1210 to placebo and 1297 to active control. Of the liraglutide-exposed patients, 3772, or 81% had type 2 diabetes mellitus. Most additional data in the safety update came from the extensions of Studies 1572, 1573 and 1807. The following table details exposure by patient-time.

Table 7.2.9.7: Extent of Liraglutide Exposure by Number of Patients and Patient-Time as of 30 May 2008 (Safety Update Cut-Off)

Type of Trial	Type of Subject	Duration of Exposure (N)						
		1 d	>1 d	≥5 wks	≥12 wks	≥24 wks	≥50 wks	≥76 wks
Single-dose	Healthy	141	147					
	DM2	47						
	Healthy Japanese	24						
Short-term (1-7 wks)	Healthy	2	162	14				
	DM2	1	62	1				
	Healthy Japanese		36	18				
	DM2 Japanese		11					
Intermediate-term (8-20 wks)[1]	DM2		526	475	333			
	DM2 Japanese		180	177	174			
	Obese nondiabetic	2	369	349	329	1		
Longterm (≥26 wks)	DM2	7	2494	2339	2222	2085	840	495
	DM2 Japanese	1	443	427	419	326		
Total Patients	Any	225	4430	3800	3477	2412	840	495
Total Patient-Years	Any	0.6	2433.8	2406.0	2356.6	2015.3	1224.2	780.2

Source: Applicant's Table 1-5, pg 21, Safety Update, stamp date 23 Sep 2008
1 The applicant included Study 1499, which was a 5-week trial

One additional death was reported in a liraglutide-treated patient with the safety update; this is the patient who died of acute pancreatitis who is further discussed in Section 7.1.1.

Information regarding thyroid cancer, MACE, and pancreatitis from the safety update was integrated into the relevant sections of the review. Data from the safety update regarding immunogenicity or injection site reactions were similar to those presented in the original NDA.

Please see Section 7.1.11 for a discussion of an imbalance in serious neoplasm events that was noted in the original NDA. In the safety update, serious malignant neoplasm events were reported for an additional 7 liraglutide-treated patients and 1 comparator-treated patient. The events in liraglutide-treated patients were breast cancer, colon cancer (3 patients), papillary thyroid cancer, adenocarcinoma pancreas and "metastases to liver". The event in a comparator-treated patient was "metastatic neoplasm". The updated rates of serious adverse events of neoplasm were 12.3 and 8.1 events per 1000 patients years for LGT and comparator, respectively. When one considers only malignant neoplastic events, the updated totals of patients with events were 26 for LGT and 10 for comparator (10.7 versus 8.1 events per 1000 patient-years). Removal of the papillary cancer event changed the rate ratio to 10.3 versus 8.1 events per 1000 PY.

Otherwise, data submitted in the safety update did not identify new safety concerns that were not noted in the original NDA submission.

7.2.9.8 Population Pharmacokinetic Data (3 Oct 2008)

These data had been requested by Dr. Khurana, and were used for his Clinical Pharmacology Review.

7.2.9.9 Re-analyses of Major Adverse Cardiovascular Events (7 Oct 2008)

In the first set of MACE analyses submitted by the applicant, events had been included that did not seem to represent cardiovascular death, MI or stroke. For example, acute renal failure, and isolated ECG findings, were included. The Agency had requested that the applicant resubmit analyses without these and some other specified terms that did not appear likely to represent the MACE of interest. This resubmission included those new analyses. For review of these data, see Section 7.1.3.3.1.

7.2.9.10 Clarifications Regarding MACE Analyses (14 Oct 2008)

This submission included clarifications regarding the revised MACE analyses that had been submitted on 7 Oct 2008. These are reviewed in Section 7.1.3.3.1.

7.2.9.11 Tabular Summaries of MACE (6 Nov 2008)

In response to a request by the Agency, the applicant provided tabular summaries of MACE events by study arm in each Phase 2/3 study. These data were reviewed for Section 7.1.3.3.1.

7.2.9.12 Surgical Pathology Reports for Cases of Thyroid Cancer (14 Nov 2008)

In response to a request from the Agency, the applicant provided surgical pathology reports for cases of thyroid cancer. These are reviewed in Section 7.1.3.3.2.

7.2.9.13 Response to Deficiencies Noted on Inspection (17 Dec 2008)

The FDA had conducted an inspection and noted deficiencies at Novo's Plainsboro, New Jersey facility. This submission included Novo's responses to those deficiencies. Ms. Jeanne Denes, the FDA inspector, found the applicant's responses satisfactory (email 13 Jul 2009).

7.2.9.14 Response to Requests from Chemistry, Manufacturing and Controls Reviewer (19 Dec 2008)

This submission included carton and container labeling, and other data requested by the CMC reviewer. Data were used for his review.

7.2.9.15 Acknowledgment of Upcoming International Inspection (23 Dec 2008)

Novo acknowledged a notification that FDA would be inspecting a clinical investigation site at Lund University Hospital in Lund, Sweden.

7.2.9.16 Population Pharmacokinetic Model Used for Study 1573 (23 Dec 2008)

This model was requested by the Clinical Pharmacology reviewer, and was used in his review.

7.2.9.17 Request for Meeting with Division Regarding Proposal for Postmarketing Cardiovascular Outcomes Study (24 Dec 2008)

Novo requested a meeting regarding a proposed CV outcomes study. However, the Division was in the process at that point of preparing the "Uniform MACE Request", and felt that it was important to obtain these additional analyses prior to providing feedback regarding the design of a cardiovascular outcomes trial. Therefore, the meeting request was denied.

7.2.9.18 Datasets for Study 1571 (14 Jan 2009)

These datasets were requested by the Clinical Pharmacology reviewer, and were used in his review.

7.2.9.19 Table of Adverse Events for All Completed Trials (16 Jan 2009)

In the original NDA submission, the applicant had not submitted a table of adverse events for all completed trials. After a request from the Division, the applicant submitted the table. The cover letter from the applicant states that the table is for all serious adverse events, but that is an error.

The original NDA did contain a table of serious adverse events for all completed trials. This submission contains a 100-page table of all adverse events, by System Organ Class and Preferred Term, as requested. These data are reviewed in Section 7.1.5.4, and in portions of Section 7.1.3.3.

7.2.9.20 Response to Request for "Uniform MACE Analyses" (21 Jan 2009)

As discussed in Section 7.1.3.3.1, the Division had made a "uniform" MACE information request of all 3 applicants who had pending applications for diabetes drugs. This submission includes Novo's response, and is reviewed in Section 7.1.3.3.1.

7.2.9.21 Response to Deficiencies in CMC Discipline Review Letter (11 Feb 2009)

This submission was reviewed by the CMC reviewer.

7.2.9.22 Responses to FDA Questions Regarding MACE Analyses from 21 Jan 2009 Submission (13 Feb 2009)

In this submission, Novo provided estimated time to event data, which had been missing from the 21 Jan 2009 submission for some patients. It had also been noted in the 21 Jan 2009 submission that it appeared that the applicant had omitted at least one stroke event that should have been included in the analyses. The applicant stated that this was because of differences between British English spelling (used in MedDRA Preferred Terms) and U.S. English spelling (used in the FDA request, and in all FDA documents). They added 7 additional event terms which should have been included, and provided revised analyses. These revised analyses were included in the review in Section 7.1.3.3.1.

7.2.9.23 Response to Request for Definitions of Baseline Diabetes Complications (13 Feb 2009)

In the original NDA Submission, the applicant had provided a table of baseline incidence of diabetes complications. The Division requested the definitions used for these complications. The applicant responded that a specific diagnostic definition was not given and the recording was based on the investigator's assessment.

7.2.9.24 Clarification Regarding Inclusion of Ischemic Stroke Event in MACE Analyses (20 Feb 2009)

In response to an FDA request, the applicant clarified that a particular event of ischemic stroke had been included in all analyses.

7.2.9.25 Clarification Regarding Data From Thyroid Surgical Pathology Reports (25 Feb 2009)

Novo submitted responses to questions from the clinical safety reviewer regarding missing or unreadable information in previously submitted thyroid surgical pathology reports. These data were used for the review of thyroid cancer cases in Section 7.1.3.3.2.

7.2.9.26 Amendment to Pediatric Plan (26 Feb 2009)

In the original NDA, the applicant requested deferral of study of patients ages 10-17. This later submission included a protocol for a PK/PD study to be conducted in adolescents, ages 10-17. The Division was concerned about initiation of studies in children when the risk for medullary thyroid cancer had not been fully characterized for adults. However, this proposed study had only a 3-week duration, which is unlikely to be associated with significant thyroid cancer risk. The Division requested the informed consent document, and Novo provided it. In the Division's opinion, the informed consent document's language regarding the rodent C-cell tumor findings was too technical and did not adequately represent the findings. The Division composed different informed consent language, which was transmitted to the applicant on 10 Jul 2009 (see Section 7.2.9.29 below).

7.2.9.27 Response to Deficiencies Noted in FDA Inspection of Analytic Facility in Copenhagen (27 Mar 2009)

In Jan 2009, the FDA inspected Novo's analytic facility in Copenhagen. This submission responds to deficiencies noted in that inspection.

7.2.9.28 Response to Deficiencies Noted in FDA Inspection of Analytic Facility in Lund, Sweden (30 Mar 2009)

In Jan 2009, the FDA inspected an analytic facility at Lund University Hospital in Lund, Sweden. This submission responds to deficiencies noted at that facility.

7.2.9.29 Information on Plans for Pediatric Study (17 Apr 2009)

This submission included a summary of pediatric plans, and a protocol for a [redacted] b(4)

[redacted] The Division was concerned about initiation of studies in children when the risk for medullary thyroid cancer had not been fully characterized for adults. This proposed study is longer than the previously proposed [redacted] The Division b(4)
requested the informed consent document, and Novo provided it. In the Division's opinion, the informed consent document's language regarding the rodent C-cell tumor findings was too technical and did not adequately represent the findings. Dr. Parola also felt it was important to inform patients that fibrosarcomas had also been seen in the animal studies. The Division composed different informed consent language, which was transmitted to the applicant on 10 Jul 2009. Two separate sets of language were proposed, one for short-term studies, and one for studies of ≥6 months' duration.

"For short-term trials (<6 months):

When liraglutide was given to rats and mice for most of their lifetime, it caused tumors, called "C-cell tumors", of the thyroid gland. Some of these tumors were cancers. It is not known

whether liraglutide will cause C-cell tumors or cancer in people. Short periods of treatment with liraglutide are not expected to cause these tumors in people. In mice, liraglutide also caused cancers of the skin and the area underneath the skin where liraglutide was injected. These cancers are called "fibrosarcomas". It is not known if liraglutide will cause fibrosarcomas in people. Short periods of treatment with liraglutide are not expected to cause these tumors in people.

For longterm trials (≥6 months):

When liraglutide was given to rats and mice for most of their lifetime, it caused tumors, called "C-cell tumors", of the thyroid gland. Some of these tumors were cancers. It is not known whether liraglutide will cause C-cell tumors or cancer in people. In people, C-cell cancers (called "medullary thyroid carcinoma") often make extra amounts of a hormone called calcitonin, which can be detected with a blood test. During the study, you will have blood drawn at certain times to check your level of calcitonin. If your calcitonin is high, you may need other tests to look for medullary thyroid carcinoma. People suspected of having medullary thyroid carcinoma will have an operation to take out their thyroid gland. If medullary thyroid carcinoma has not spread outside the thyroid gland, they are usually cured. In mice, liraglutide also caused cancers of the skin and the area underneath the skin where liraglutide was injected. These cancers are called "fibrosarcomas". It is not known if liraglutide will cause fibrosarcomas in people."

7.2.9.30 Request for Type A Meeting (22 Apr 2009)

After the 2 Apr 2009 Advisory Committee meeting, the applicant requested this Type A meeting, which was held on 1 Jun 2009. Data from a revised briefing document from that meeting are presented in Section 7.2.9.39 below.

7.2.9.31 Additional Responses to Deficiencies noted in FDA Inspections of Lund, Sweden, and Copenhagen Facilities (8 May 2009)

Novo provided additional responses regarding deficiencies previously mentioned.

7.2.9.32 Meeting Package for 1 Jun 2009 Type A Meeting (18 May 2009)

This was the meeting package for the 1 Jun 2009 meeting that was held with the applicant. After questions from the Agency regarding missing calcitonin data, the applicant reported a programming error that had affected multiple types of calcitonin analyses. A corrected briefing document was submitted on 8 Jul 2009, and is reviewed in Section 7.2.9.39 below.

7.2.9.33 Response to FDA Questions Regarding Case of Suspected Pheochromocytoma, Definitions for Clinically Significant Laboratory Events, and MACE in Patients Who Had Diabetes ≥ 10 Years (22 May 2009)

Novo responded to several questions in this document.

A case of suspected pheochromocytoma turned out to have normal catecholamine studies.

The original NDA had presented laboratory data as "not clinically significant" or "clinically significant", but no definition of "clinically significant" was provided. In other NDAs, the applicant typically provides a value (high and/or low) which is uniformly considered to be clinically significant across studies in their program, for hematology, chemistry and urinalysis values. However, this was not done for Novo's laboratory data. They stated that "Exact values defining clinical significance were not defined by the sponsor and the reporting of clinical significance was based on the investigator's assessment of the patient's status and the normal ranges reported for these particular analytes." In the clinical reviewer's opinion, this method may be subjective, and a request for outliers in specified ranges for certain key laboratory parameters was sent to the applicant.

At the 2 Apr 2009 Advisory Committee (AC) meeting, one of the panel members had asked Novo if MACE analyses were available by baseline duration of diabetes, specifically <10 y, or ≥10 y. This is because some recent large studies have suggested that patients who have had diabetes >10 y may not benefit, or might even be harmed (from a cardiovascular standpoint) by tight glycemic control, while those whose diabetes is of shorter duration might benefit or at least not be harmed. After the AC, the Division requested analyses from Novo regarding this question.

In the analysis population, 1024/4257 patients (24%) had had diabetes for ≥10 y at study entry. Overall, there were few events among patients who had diabetes ≥10 years.

For comparisons of liraglutide to total comparator, there was no appreciable pattern of difference between patients who had diabetes for <10 years, and those who had diabetes for ≥10 years. In addition to the Cochran Mantel Haenszel (CMH) method using the incidence ratio, the applicant also presented analyses using a CMH method for the incidence rate ratio, and a Cox Proportional Hazards model. Results were qualitatively similar.

Table 7.2.9.33.1: MACE Events by Baseline Duration of Diabetes, Liraglutide versus Total Comparator, Applicant's Analyses by Cochran Mantel Haenszel Method

Endpoint	Pop	Incidence Ratio Estimate		95% CI Upper Bound		LGT N		TC N	
		DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y
FDA Custom	A	0.90	0.39	2.33	2.01	10	3	8	5
SMQ Narrow	A	1.02	0.60	2.29	1.99	16	6	11	6
SMQ Broad	A	0.88	0.86	1.45	1.92	37	14	25	10
FDA Custom	B	0.75	0.92	1.62	3.38	14	7	12	5
SMQ Narrow	B	0.90	0.85	1.73	2.16	23	12	16	8
SMQ Broad	B	0.86	0.90	1.36	1.74	47	22	31	14

Source: Applicant's Tables 1 and 2, serial pg 9, NDA 22341 subm stamp date 22 May 2009

The following table presents data for liraglutide versus active comparator, again by baseline duration of diabetes. As with comparisons to total comparator, results are qualitatively similar for patients who had diabetes <10 years and those who had diabetes ≥10 years.

Table 7.2.9.33.2: MACE Events by Baseline Duration of Diabetes, Liraglutide versus Active Comparator, Applicant's Analyses by Cochran Mantel Haenszel Method

Endpoint	Pop	Incidence Ratio Estimate		95% CI Upper Bound		LGT N		AC N	
		DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y
FDA Custom	A	0.83	0.30	2.28	2.54	10	3	7	3
SMQ Narrow	A	0.83	0.66	1.93	3.61	16	6	10	3
SMQ Broad	A	0.77	1.01	1.33	2.64	37	14	20	6
FDA Custom	B	0.74	0.81	1.72	4.12	14	7	10	3
SMQ Narrow	B	0.78	0.96	1.57	3.48	23	12	14	4
SMQ Broad	B	0.75	1.23	1.21	2.90	47	22	25	7

Source: Applicant's Tables 3 and 4, beg serial pg 10; and Tables 8 and 9, beg serial pg 16; NDA 22341 subm stamp date 22 May 2009

The following table presents data for liraglutide versus placebo, again by baseline duration of diabetes.

Table 7.2.9.33.3: MACE Events by Baseline Duration of Diabetes, Liraglutide versus Placebo, Applicant's Analyses by Cochran Mantel Haenszel Method

Endpoint	Pop	Incidence Ratio Estimate		95% CI Upper Bound		LGT N		PBO N	
		DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y	DM <10 y	DM ≥10 y
FDA Custom	A	1.47	0.40	10.47	2.43	10	3	1	2
SMQ Narrow	A	2.66	0.46	18.15	1.81	16	6	1	3
SMQ Broad	A	1.34	0.62	3.48	2.02	37	14	5	4
FDA Custom	B	1.03	0.82	5.17	4.09	14	7	2	2
SMQ Narrow	B	1.98	0.65	9.17	2.08	23	12	2	4
SMQ Broad	B	1.44	0.61	3.51	1.54	47	22	6	7

Source: Applicant's Tables 3 and 4, beg serial pg 10; and Tables 8 and 9, beg serial pg 16; NDA 22341 subm stamp date 22 May 2009

Point estimates of >1, and high upper bounds of the 95% confidence interval are noted for some comparisons of liraglutide to placebo, particularly in the analyses of patients who have had diabetes for <10 years. However, all confidence intervals included 1, and thus the differences are not statistically significant. High upper bound estimates are likely related to very low event numbers for the placebo groups. As previously discussed, point estimates of >1 for liraglutide versus placebo among patients with diabetes <10 years are not likely to be related to differences in baseline cardiovascular risk factors between liraglutide and placebo group patients. These elevated point estimates are not an expected finding, but are difficult to interpret in the setting of such low event rates.

Overall, for these analyses, low event numbers limit interpretability for analyses of risk for MACE by baseline diabetes duration.

7.2.9.34 Response to Request for Information Regarding Elevated Bilirubin Levels (28 May 2009)

Because there was a numerical imbalance in cases of "clinically significant" elevations of bilirubin levels, not favoring liraglutide, but "clinically significant" was not defined, the clinical safety reviewer had requested that the applicant provide the number and percentage of patients in each treatment group in the Phase 3 trials who had bilirubin elevations >2x, >3x and >10x ULN, etc. In this submission, the applicant replied that no patients had elevations >2x ULN. However, as mentioned above in Section 7.1.7.3.2, at least two patients had bilirubin elevations >5x ULN. On 14 Jul 2009, the Division requested further clarification.

7.2.9.35 Responses to Questions Regarding Impurities in Genetic Testing Material, and Historical Control Data for Embryofetal Development Toxicology Studies (22 Jun 2009)

Dr. Parola requested this information, and used it in his review.

7.2.9.36 Response to Questions Regarding Missing Calcitonin Data, Numbers of Completers for 52 Week and 104 Week Extension Data, and Numbers of Patients Who Developed Calcitonins ≥20 ng/L and ≥50 ng/L (25 Jun 2009)

In response to a query from the Agency regarding missing calcitonin values from shift tables in the meeting package for the 1 Jun 2009 meeting, the applicant replied that there had been a programming error that had affected calcitonin tables, figures and analyses in that document. The full corrected document is reviewed in Section 7.2.9.39. The data for the numbers of patients with calcitonins ≥20 and ≥50 are in Section 7.1.3.3.2.4.

7.2.9.37 Responses to Queries Regarding Completer Analyses of Efficacy versus Exenatide, and a Patients Who had RET Proto-oncogene Testing (25 Jun 2009)

Dr. Yanoff had requested clarification regarding completer analyses from the preliminary data for the LGT versus exenatide study. Data from the patient who had RET testing done are presented in Section 7.1.3.3.2.

7.2.9.38 Pharmacokinetic Exposure Data for Obese Patients (25 Jun 2009)

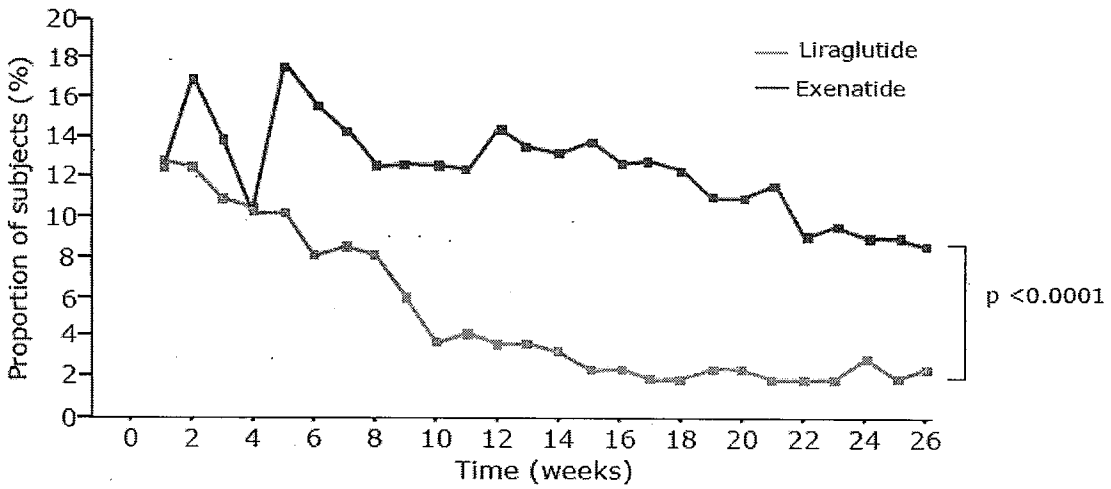
These data were requested to determine if exposure to the 3 mg dose in obese patients would result in higher liraglutide blood levels than would exposure to the 1.8 mg dose in patients in the diabetes trials. These data are reviewed in Section 7.2.9.39.

7.2.9.39 Corrected Briefing Document for 1 Jun 2009 Meeting (8 Jul 2009)

On 1 Jun 2009, Novo met with the Division to present an update on the efficacy and safety of liraglutide with information that was newly available after the 2 Apr 2009 Advisory Committee meeting. After the meeting, however, in response to an inquiry from the Division regarding missing calcitonin data, the applicant noted that a programming error had occurred for some of the calcitonin analyses. Novo notified the Division of this programming error on 25 Jun 2009. A corrected briefing document was submitted on 8 Jul 2009. Updated safety information from that document is included in this section.

The applicant provided preliminary safety information from Study 1797, a trial of liraglutide versus exenatide. Full data from this trial were not available for review. In that study, after 4 weeks of therapy, patients treated with liraglutide were less likely to report nausea than were patients treated with exenatide, as illustrated in the following figure. This figure was presented in color in the submission; if it is viewed in black and white, the upper curve is the exenatide curve.

Figure 7.2.9.39.1: Proportion of Subjects Reporting Nausea Over Time, Study 1797



Data are number (%) of patients exposed to treatment (safety population)

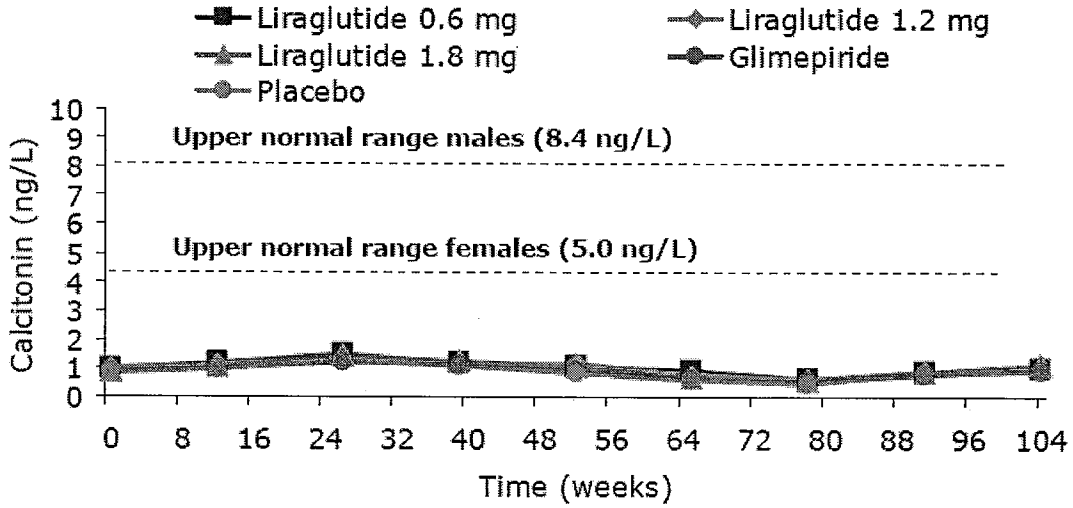
Source: Applicant's Figure 13, serial pg 37, NDA 22341 submission 8 Jul 2009

In Study 1797, 58% of exenatide-treated patients developed anti-exenatide antibodies, while 2% of liraglutide-treated patients developed anti-liraglutide antibodies. Data were not presented regarding cross-reactivity with native GLP-1, or neutralizing effect.

Several updated calcitonin analyses were presented.

Two-year extension data, from Studies 1572 and 1573, showed that mean calcitonin levels remained near the lower limit of quantitation over time, as shown in the following figure of data from Study 1572.

Figure 7.2.9.39.2: Geometric Mean Calcitonin Values Through Two Year Extension Data, Study 1572



Source: Applicant's Figure 18, pg 55, NDA 22341 submission stamp date 8 Jul 2009

It should be noted that the dropout rate for extension studies of liraglutide was high, and somewhat different between treatment groups, as shown in the following table.

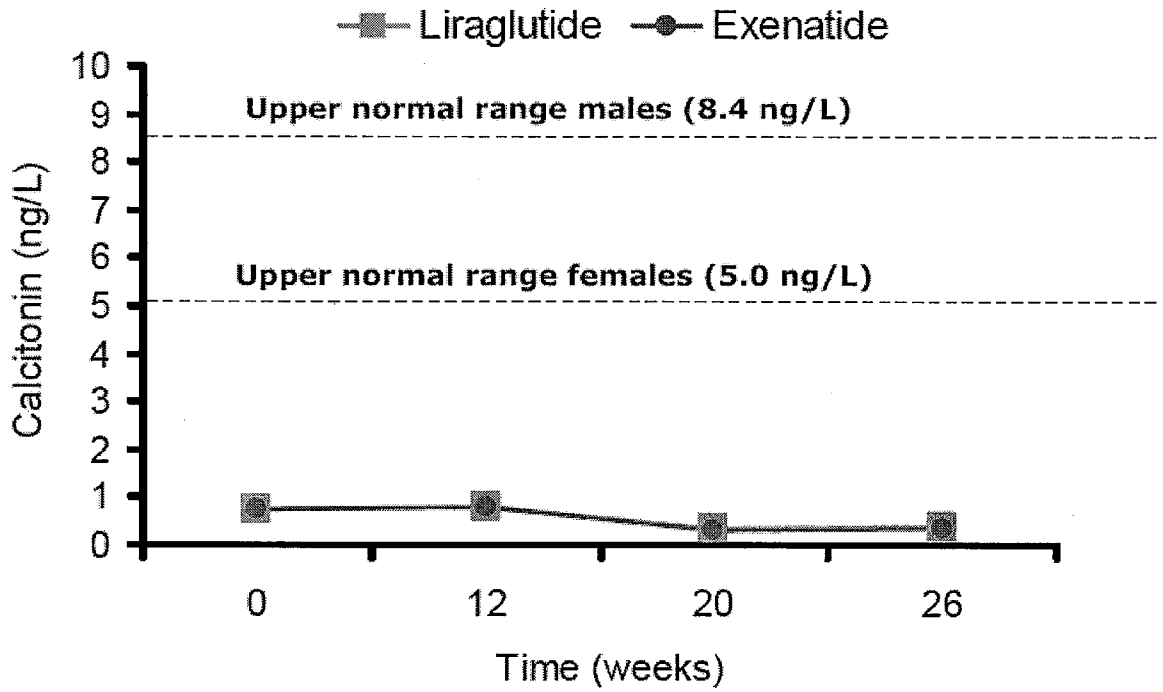
Table 7.2.9.39.1: Percent Dropouts at 12 and 24 Months, Phase 3 Trials of Liraglutide

Time Point	LGT	PBO	AC
12 mo (5 trials)	41%	66%	49%
24 mo (2 trials)	50%	74%	57%

Source: Applicant's Table 1, serial pg 6, NDA 22341 submission stamp date 25 Jun 2009, and Table 4.2.2 above

Mean serum calcitonin out to 26 weeks was similar for liraglutide and exenatide in preliminary information from Study 1797, as shown in the following figure.

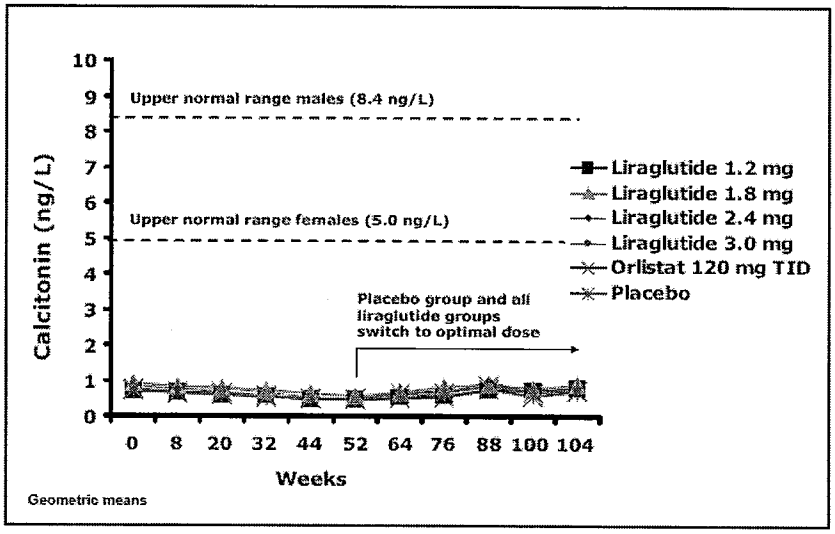
Figure 7.2.9.39.3: Geometric Mean Calcitonin over 26 Weeks, Study 1797



Source: Applicant's Figure 19, pg 55, NDA 22341 submission stamp date 8 Jul 2009

Preliminary data were provided for Study 1807, a Phase 2 trial for liraglutide in the treatment of obesity. Full study data were not available for review. The main trial duration was 20 weeks, with a planned 84 week extension. In that study, mean calcitonin values out to 104 weeks were similar for liraglutide versus orlistat or placebo.

Figure 7.2.9.39.4: Geometric Mean Calcitonin Extension Data Out to 104 Weeks, Obesity Study 1807



Data are presented based on original randomized treatment groups. At Week 52, subjects in the liraglutide and placebo groups were switched to receive an 'optimal' dose of liraglutide; subjects in the orlistat group continued with orlistat. The optimal dose of liraglutide was determined to be 2.4 mg at the beginning of the open-label extension period and then escalated to 3.0 mg based on the results of the 52-week interim analysis. The switch to the 3.0 mg dose was not done at a specific visit and the calendar date for change from 2.4 mg liraglutide to 3.0 mg liraglutide was not the same for all subjects, but was within a few months. Due to the gradual switching of subjects, the time of exposure to 2.4 mg liraglutide and 3.0 mg liraglutide is therefore not the same for all subjects.

Source: Applicant's Figure 21, pg 56, NDA 22341 submission stamp date 8 Jul 2009

In this trial, 93 of the subjects were randomized to a liraglutide dose of 3 mg. Pharmacokinetic exposure to liraglutide declines with increasing body weight, but the 3 mg dose in obese subjects does result in somewhat higher PK exposure than does the 1.8 mg dose in patients with type 2 diabetes mellitus (NDA 22341, submission stamp date 25 Jun 2009). The percentage of dropouts was not provided for this trial.

Data were provided regarding mean calcitonin over time for patients who had elevated baseline calcitonin in the Phase 3 Trials. Among these patients, mean calcitonin levels did not tend to increase further over time (Source: Applicant's Tables 1-5, beginning pg 101, NDA 22341 submission stamp date 8 Jul 2009).

Over time, post-baseline elevations of calcitonin were not uniformly persistent in trials that had data out to 52 weeks (1573, 1700, 1701, 1572 extension, 1807 extension preliminary data). The following table illustrates this.

Table 7.2.9.39.2: Number and Percentage of Patients with Post-Baseline Persistently Elevated Calcitonin

Timepoint to Which Post-Baseline Elevation of Calcitonin Persisted	LGT Male N[1]=812 n (%)	LGT Female N[1]=785	PBO Male N[1]=104	PBO Female N[1]=101	AC Male N[1]=312	AC Female N[1]=292
Wk 12 LOCF	24 (3.0)	4 (0.5)	1 (1.0)	1 (1.0)	8 (2.6)	3 (1.1)
Wk 20/24/26/28 LOCF	14 (1.7)	2 (0.3)	0	0	6 (1.9)	2 (0.7)
Wk 52 LOCF	8 (1.0)	1 (0.1)	0	0	5 (1.6)	1 (0.4)

Source: Applicant's Table 45, serial page 156, NDA 22341 submission stamp date 8 Jul 2009
1 N = number of patients with baseline calcitonin ≤ULN

Results of a repeated measures analysis comparing liraglutide to metformin, and liraglutide to all active comparator, showed a statistically significant mean difference in percent change in calcitonin, not favoring liraglutide, at Week 12, for all doses and comparisons. At Week 26, this difference remained significant for comparisons of metformin to the liraglutide 1.2 and 1.8 mg doses, but for total comparator, remained significant only for comparison to the 1.8 mg dose. Analyses beyond 26 weeks were not provided.

Table 7.2.9.39.3: Repeated Measurement Analysis for Calcitonin, Combined Data from Studies 1572, 1573, 1436, 1574 and 1697

Week	Comparison	Estimate (95% CI)	p-value
12	LGT 1.8 vs. MET	10.8 (3.3, 18.9)	0.0042
	LGT 1.2 vs. MET	13.3 (5.3, 22.0)	0.0008
	LGT 0.6 vs. MET	13.1 (4.1, 22.9)	0.0036
	LGT 1.8 vs. all AC	8.5 (2.3, 15.0)	0.0063
	LGT 1.2 vs. all AC	10.9 (4.2, 18.0)	0.0011
	LGT 0.6 vs. all AC	10.7 (2.9, 19.1)	0.0064
26	LGT 1.8 vs. MET	12.1 (4.3, 20.5)	0.0018
	LGT 1.2 vs. MET	9.4 (1.5, 17.9)	0.0189
	LGT 0.6 vs. MET	6.2 (-2.4, 15.5)	0.1646
	LGT 1.8 vs. all AC	6.7 (0.7, 13.2)	0.0281
	LGT 1.2 vs. all AC	4.2 (-2.1, 10.8)	0.1995
	LGT 0.6 vs. all AC	1.1 (-6.0, 8.8)	0.7732

Source: Applicant's Table 51, serial pg 212, NDA 22341 submission stamp date 8 Jul 2009

Elements of a proposed risk management plan were also submitted, and are discussed further in section 8.7.

7.2.9.40 Draft Medication Guide and Risk Evaluation and Mitigation Strategy (8 Jul 2009)

The Risk Evaluation and Mitigation Strategy consists of a proposed Medication Guide. The draft Medication Guide is reviewed in Section 9.4.

7.2.9.41 Responses Regarding Information Requests for Bilirubin and Creatinine Data

These responses are reviewed in Section 7.1.7.3.3.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See Sections and 7.4.3 and 9.1.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

For purposes of safety evaluation, pooling of data was used. In general, the set of all completed Phase 2 and Phase 3 trials was used. For some analyses, the set of the 5 main Phase 3 trials was used. For the analyses of Major Adverse Cardiovascular Events, data were stratified by study.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Explorations for dose-dependence were carried out for multiple adverse events. The following observations of dose-dependence were noted:

- In the 5 major Phase 3 trials, the incidence of gastrointestinal adverse events was dose-related. This was also true for withdrawal due to GI events.
- In the 5 major Phase 3 trials, the applicant stated that adverse events related to immunogenicity appeared dose-dependent. However, this relationship was not as clear to the clinical safety reviewer,
- In the 5 major Phase 3 trials, the incidence of injection site reactions appeared to be dose-dependent.
- In Japanese Study 1334, there was a dose-dependent increase in blood eosinophil levels.
- In the 5 major Phase 3 trials, from baseline to 26-28 weeks (end of blinded period for 4/5 trials), there was a dose-dependent trend for women to shift from calcitonin values below the lower limit of quantitation to within the range of quantitation. This trend was not noted for men, and was not noted at some observation points in the extensions (after unblinding).
- In the 5 major Phase 3 trials, at 12 weeks, calcitonin relative differences for LGT versus PBO were statistically significant, not favoring LGT, and were dose-dependent. For LGT versus AC, differences did not favor LGT and were dose-dependent, but were not statistically significant. This dose-dependent trend was not seen in some unblinded extension observations.

- In the 5 major Phase 3 trials, the highest percentage of upward shifters in calcitonin category was in the 1.8 mg LGT dose group, which is the highest dose group being considered for approval.
- In the set of all completed Phase 3 trials of LGT as of 24 Jun 2009, the highest percentage of patients who had a baseline calcitonin <20 ng/L and later developed a calcitonin >20 ng/L was in the 1.8 mg LGT dose group.

7.4.2.2 Explorations for time dependency for adverse findings

As discussed in Section 7.2.9.39, in preliminary data from a trial of liraglutide versus exenatide, after 4 weeks of treatment, patients treated with liraglutide were less likely to report nausea than were patients treated with exenatide.

7.4.2.3 Explorations for drug-demographic interactions

In general, women reported adverse events at a higher rate than men.

In the 5 major Phase 3 trials, women were more likely than men to begin with a serum calcitonin value below the lower limit of quantitation. Also, from baseline to 26-28 weeks (end of blinded period for 4/5 trials), there was a dose-dependent trend for women to shift from calcitonin values below the lower limit of quantitation to within the range of quantitation. This trend was not noted for men, and was not noted at some observation points in the extensions (after unblinding).

Patients of Hispanic/Latino ethnicity had a lower overall rate of reported adverse events that did patients who were not of this ethnic group. In LGT-treated patients, the incidence of reported adverse events was 72.3% for Hispanic/Latino patients and 89.2% for patients of other ethnic groups. For comparator-treated patients, the rates were 65.6 and 77.1%, respectively. No one type of event appeared to account for this difference. Otherwise, there were no differences by racial or ethnic group.

Few patients ≥age 75 years were studied, and conclusions cannot be reached regarding interactions between age and the safety of liraglutide in persons this age and older. Patients age ≥65 years were not more likely overall to experience adverse events than were patients <age 65 years.

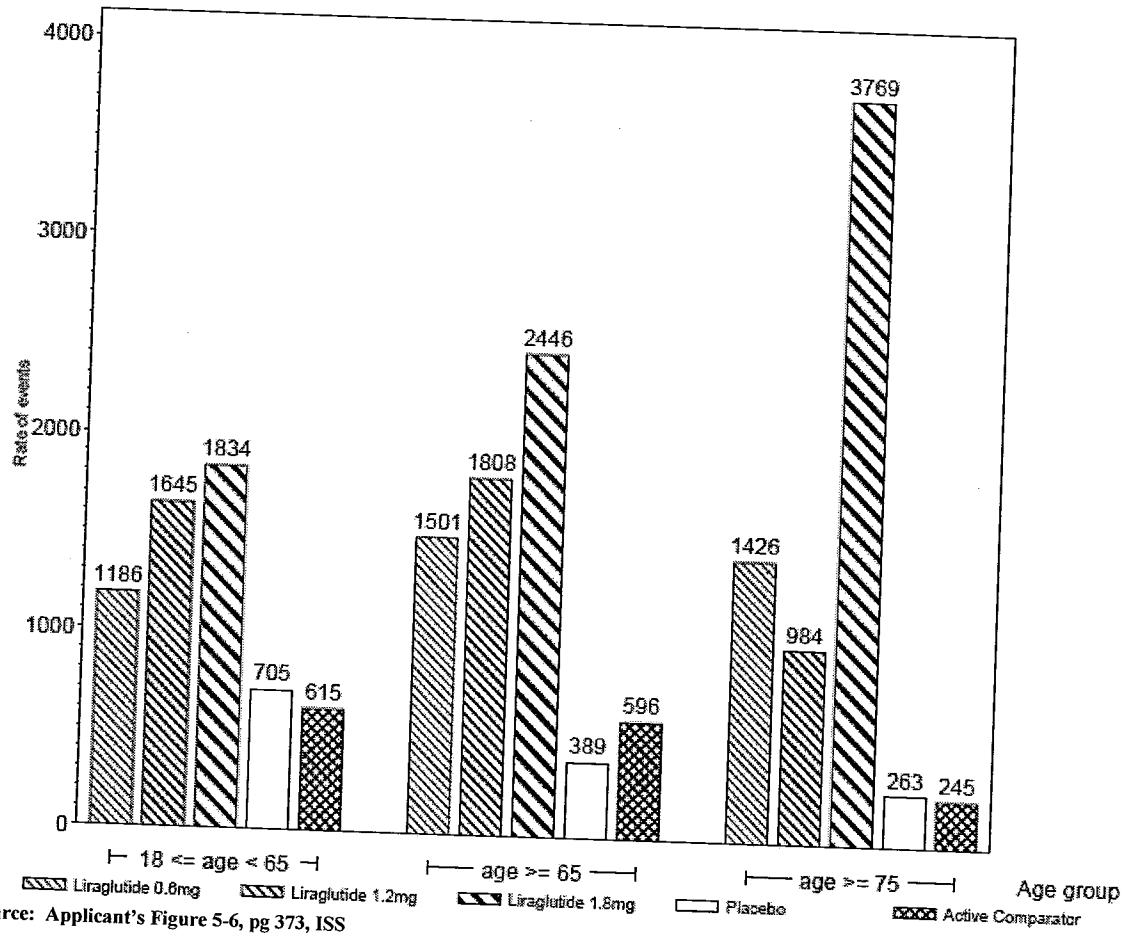
Table 7.4.2.3.1: Incidence of Adverse Events by Age, 5 Major Phase 3 Trials at Time of NDA Submission

	Age <65 Yrs		Age ≥65 Yrs N		Age ≥75 Yrs	
	LGT	Non-LGT	LGT	Non-LGT	LGT	Non-LGT
N	1993	1188	508	289	66	47
n	1519	803	391	174	48	29
%	76.2	67.6	77.0	60.2	72.7	61.7

Source: Applicant's Table 5-2, pg 371, ISS

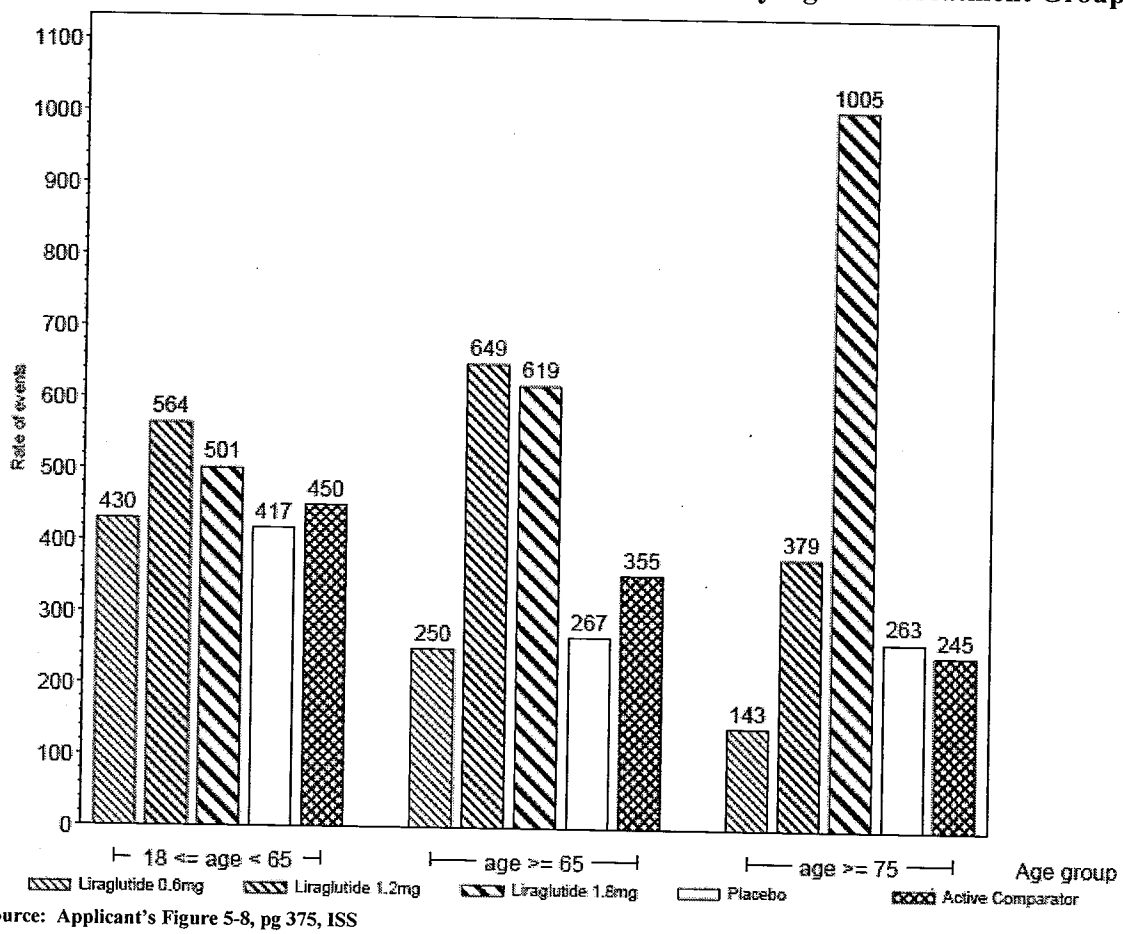
For the 1.8 mg LGT dose, the rates of gastrointestinal and nervous system adverse events increased with age. This was not seen for comparator-treated patients, as illustrated in the following two figures.

Figure 7.4.2.3.1: Rate of Gastrointestinal System Adverse Events by Age and Treatment Group



Source: Applicant's Figure 5-6, pg 373, ISS

Figure 7.4.2.3.2: Rate of Nervous System Adverse Events by Age and Treatment Group



Source: Applicant's Figure 5-8, pg 375, ISS

7.4.2.4 Explorations for drug-disease interactions

Please see Section 5 for a discussion of the use of liraglutide in patients with decreased hepatic or renal function. Please see Section 7.2.9.33 for an analysis of the incidence of MACE by baseline duration of diabetes.

7.4.2.5 Explorations for drug-drug interactions

See Section 8.2 for a discussion of drug-drug interaction studies.

See Section 7.1.3.3.5 for a discussion of serious hypoglycemic events. All serious hypoglycemic events in the Phase 3 trials of liraglutide occurred among liraglutide-treated patients. Of the 9 patients who had a serious hypoglycemic event, 6 were taking a concomitant sulfonylurea.

7.4.3 Causality Determination

Gastrointestinal events (particularly nausea, vomiting and diarrhea), injection site reactions, dizziness and fatigue are likely causally related to the use of liraglutide.

Numerical imbalances also exist for papillary thyroid cancer, C-cell hyperplasia events, pancreatitis, serious hypoglycemia events, events related to increased heart rate, events potentially related to immunogenicity, and overall malignancies. However, due to the low number of events for the former 5, and the relatively small imbalance for immunogenicity-related events and overall malignancies, causality cannot be definitively assigned.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Please see Dr. Yanoff's clinical efficacy review.

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed tradename (Victoza®), and had no objection. CDR Walter Fava of DMEPA notified Dr. Bishai, the Project Manager, of the tradename evaluation conclusions by email on 8 Jul 2009.

8.2 Drug-Drug Interactions

See Dr. Khurana's review for discussion of the pharmacokinetic drug-drug interaction studies that were performed.

Liraglutide's effect on metabolism by multiple cytochrome P450 isoforms was investigated, and liraglutide had little effect. It is metabolized by DPP4, and by other peptidases.

Liraglutide slows gastric emptying, and thus may prolong Tmax, and lower Cmax of orally administered drugs. Liraglutide delayed Tmax and lowered Cmax for atorvastatin, lisinopril, paracetamol and digoxin. For griseofulvin, however, Cmax was 37% higher at liraglutide steady state conditions when compared to placebo. The clinical significance of this effect is under discussion with the Clinical Pharmacology team.

No drug-drug interaction study with warfarin was performed. There have been postmarketing reports of possible warfarin interactions with exenatide. The Clinical Pharmacology team is discussing whether a warfarin interaction study would be advisable for liraglutide.

8.3 Special Populations

Dosage adjustment does not appear necessary for patients with hepatic or renal impairment. There were too few patients age 75 years or older to make conclusions regarding dosing in this

population; the 1.8 mg dose may be associated with more gastrointestinal and nervous system adverse events in this age group than in younger patients. No dosage adjustment appears necessary by race or ethnicity. As discussed earlier, Pregnancy Category C is recommended, and use in nursing mothers is not recommended. It is not known if liraglutide is present in human milk, but it does appear in the milk of lactating mice at about 50% of plasma levels.

8.4 Pediatrics

In the original NDA submission, the applicant requested deferral of the requirement to study patients ages 10-17 years, and a waiver of the requirement to study patients <10 years of age. The applicant later submitted protocols for a PK/PD study in patients ages 10-17 years, and a 14 week efficacy and safety study with a 38 week extension, to be conducted in patients ages 10-17 years. The Division had concerns about the adequacy of the informed consent for these studies; please see Section 7.2.9.29 for revised wording that was requested.

The applicant continues to request a waiver for study of patients with type 2 diabetes who are below 10 years of age. Their waiver request cites Section 505B(a)(4)(B)(i) of the Food, Drug and Cosmetic Act, and states that pediatric studies in this age group for this indication are impossible or highly impractical. Type 2 diabetes mellitus typically has its onset after the onset of puberty. Novo cites CDC data (CDC 2005) showing that, in 2005 in the U.S., about 176,500 people under age 20 years had type 2 diabetes. Of these, 0.22% were under age 10 years. A recent epidemiologic study (Dabalea 2007) estimates approximately 2 cases per 100,000 children in this age group in the U.S..

In the clinical safety reviewer's opinion, this waiver would be appropriate.

8.5 Advisory Committee Meeting

On 2 Apr 2009, data regarding Major Cardiovascular Adverse Events, preclinical rodent C-cell tumors, human thyroid cancer and human calcitonin were presented to the Metabolic and Endocrine Drugs Advisory Committee Meeting. The Agency did not present efficacy data, and did not request discussion of efficacy data. Also on the panel were two cardiologists. The panel included two experts on thyroid cancer, Dr. Kenneth Burman and Dr. Michael Tuttle. Dr. Burman chaired the Committee. After presentations from the applicant and the Agency and discussion by the committee, the committee was asked to vote on several questions. These questions, the outcome of each vote, and a summary of explanatory comments from Committee members regarding each vote, follow.

Cardiovascular Question 1. Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that liraglutide rules out unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?

Vote: 8 "yes", 5 "no". Both cardiologists on the panel voted "no", as did the biostatistician on the panel.

Dr. Konstam, one of the cardiologists, explained his "no" vote by stating that he felt that tighter confidence boundaries were needed for an adequate degree of certainty. He was also concerned about the relatively low risk population that was studied. He also felt that the more specific "FDA Custom" endpoint was more meaningful than broader endpoints. He noted that several of the upper bounds of 95% confidence intervals were near 1.8, and stated that he did not feel that this met "the spirit of the guidance document". He stated, however, that if this drug represented a major clinical advance for diabetes care, he might be willing to accept some level of risk. He felt that, going forward, another trial is needed, which could perhaps be combined with the existing data using Bayesian methods.

Dr. Teerlink, one of the cardiologists, voted "no". He expressed concerns about a duty to protect the public health and stated "I don't think we have the data here to do that adequately". He was concerned that "we have 40 events to try to determine whether there is going to be a long-term adverse outcome of a drug that's going to be given to millions of United States citizens and throughout the world". He expressed concerns about "very, very low event numbers, in addition to non-adjusted, non-adjudicated events, but in addition to that, we now have a non-consistent confidence interval and point estimates that are susceptible to which study groups we look at. Even within the one, the upper bound is nudging 1.8. Then you have an unblinded follow-up here that actually contributes most of the events."

Dr. Proschan, the biostatistician, explained his "no" vote by stating that he did not feel that the applicant had ruled out the possibility of an unacceptable excess cardiovascular risk. He stated that he was also "troubled by other things like the fact that the relative risk versus placebo was greater than the relative risk versus comparators".

Dr. Wyne, an endocrinologist, voted "no". She stated that the applicant and the Agency "just simply don't have the information to answer that question".

Dr. Henderson, the Consumer Representative, voted "no", "but with a heavy heart". She stated that she was "not 100% confident that the risk was ruled out".

Dr. Burman, one of the thyroid cancer experts, voted "yes". He stated that he felt that the analyses versus total comparator were within the guidelines regarding the 1.8 upper limit. He noted caveats regarding lack of adjudication of events, small numbers of events, and relatively short studies. He stated it would be very important for postmarketing study to be done.

Dr. Flegal, an Epidemiologist, voted "yes", "also with a heavy heart". She stated that she based her decision primarily on the results versus total comparator in Population A. She had concerns about the small number of events, but stated that the point estimates were favorable and noted that there will be further study done.

Dr. Felner, a pediatric endocrinologist, voted "yes". He noted that this application came in before the Cardiovascular Risk Evaluation guidance was released. He stated he felt the applicant had done everything that they were supposed to do, as best they could, given the retrospective

look at the cardiovascular risk. He stated that he thought the drug has great potential, especially if it's used early in the condition. He stated that he wishes to use it to treat children early in their diabetes.

Dr. Tuttle, one of the thyroid cancer experts, voted "yes". He stated that he didn't think it was fair to change the rules "once we are through". He said that he thought unacceptable excess cardiovascular risk was ruled out in the population that was studied.

Dr. Savage, an endocrinologist, voted "yes", "but with considerable reservations". He was concerned that the studies had excluded patients with cardiovascular disease. He thought there should be restrictions on the use of the drug until there is more certainty about whether it is safe in patients who are high risk for cardiovascular disease.

Dr. Levitsky, a pediatric endocrinologist, voted "yes". She felt that the studies met the guidelines, and stated that there will need to be follow-up studies.

Dr. Lesar, a Pharmacologist, voted "yes", but stated that it was a "troubled yes". He was concerned about the low number of events, the results for the placebo comparator, and the sensitivity to analysis method. He was somewhat reassured by the results versus total comparator.

Ms. Killion, the Patient Representative, voted "yes". She felt that the FDA guidelines were satisfied.

Thyroid Question 1. Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans?

Vote: 1 "yes", 12 "no". Both thyroid cancer experts voted "no".

Dr. Wyne voted "yes". She felt that the receptor-binding data suggested that the effect in humans might not be the same as in rodents.

All other Committee members voted "no". Their comments follow.

Dr. Tuttle, one of the thyroid cancer experts, stated that the data did not allow him to comfortably rule out an effect in humans. He stated that he would not be surprised if people who are exposed to the drug for "years and years and years" develop C-cell hyperplasia and maybe even medullary thyroid cancer. He also expressed concerns about risk associated with screening studies and surgery. He stated that "as much as I would dislike it" he would do a screening calcitonin and ultrasound and follow them annually. He would be uncomfortable following a patient without these tests.

Dr. Burman, one of the thyroid cancer experts, stated that the issue of calcitonin elevations in humans and C-cell hyperplasia and adenomas and cancers in rodents is "unsettling". He noted that mild calcitonin elevations can be non-specific. He stated it is impossible at present to know

whether increased serum calcitonin levels in this setting will be a harbinger of C-cell hyperplasia and ultimately medullary carcinoma in RET-negative individuals. He stated that, in RET-positive individuals, progression from CCH to MTC does occur, but it is not known with certainty whether this progression (from CCH to MTC) occurs in RET-negative individuals. He stated that the human clinical studies do not adequately address the question of elevated calcitonin due to small numbers of cases and relatively short follow-up. He stated that "our goal is to err on the side of caution regarding possible adverse events for the population even if the drug may be efficacious, especially in this clinical context".

Dr. Flegal stated that human relevance could not comfortably be ruled out, since the animal findings were in two species and two genders. She also expressed concern about increased risk of screening.

Dr. Lesar stated that there were not enough human data to suggest that the animal findings are not important. He "was not totally convinced by the mechanistic explanation that was used" by the applicant.

Dr. Savage stated that the animal data were worrisome and the he "didn't see sufficient human data to feel reassured". He stated that he was not convinced that the benefit of the drug outweighs the tradeoffs, "probably not so much in terms of metastatic cancer, but the extra burden on patients, unnecessary surgery and all these things that came up in the discussion".

Dr. Konstam stated that, even if the applicant and the Agency had agreed on the mechanistic hypothesis, that would still not have assured him that this is not clinically relevant.

Dr. Teerlink expressed a concern that what is known about the natural history of medullary thyroid cancer in humans might not translate into the same kind of activity in a drug-induced MTC.

Dr. Levitsky expressed a concern about giving liraglutide to young adults who have the potential for a very long exposure to the drug.

Dr. Felner stated that he was uncertain of the role of calcitonin screening or RET proto-oncogene testing in patients in this setting.

Dr. Henderson stated that one simply can't dismiss the data from the rodents.

Dr. Proschan stated his reasons were similar to those previously stated by other panel members.

Ms. Killion expressed concerns about the number of unknowns, and expressed interest in further study.

Thyroid Question 2. Assuming the remainder of the risk:benefit data are acceptable, do the available data on thyroid C-cell tumors permit marketing of liraglutide?

Vote: 6 "yes", 6 "no", 1 "abstain". One thyroid cancer expert voted "no" and one voted "yes".

Dr. Tuttle, one of the thyroid cancer experts, voted "yes". He stated this was primarily because "I can't think of two more years worth of data I can send the Sponsor back to that's going to make me happy." He further stated, "I suspect unfortunately the only way we are going to know this answer is to expose a large part of the population for 10 or 15 years, and that's probably where we will really find out whether we see some C-cell hyperplasia." He stated that the one- and two-year data did not look "like it's causing tremendous problems early on".

Dr. Henderson voted "yes". She felt that this was a manageable risk, not a sudden onset risk.

Dr. Felner voted "yes". He felt the risk could be managed by screening for family history, calcitonin trends, and possibly the RET proto-oncogene.

Dr. Levitsky voted "yes". She stated that, in the age range she deals with (pediatric patients), thyroid carcinomas are not common. She felt that one would have to conduct a very large study to find medullary thyroid cancer.

Dr. Wyne voted "yes". She felt that the human signal was low, and that the risk was manageable and monitorable. She felt that the proposed postmarketing cardiovascular outcomes trial could provide additional information.

Ms. Killion voted "yes". She stated she thought the risks were manageable.

Dr. Burman, one of the thyroid cancer experts, voted "no". He stated that he believed more information could be obtained through a clinical study that included monitoring of calcitonin, procalcitonin, CEA, sonograms, and perhaps calcium stimulation testing, although he felt that the latter was less sensitive. He stated that perhaps 6-12 months' longer observation than in the currently available trial data could provide some reassurance. He noted that the observed calcitonin elevations in humans were not in the range that would generally be considered clinically significant in the majority of patients.

Dr. Proschan voted "no", but wondered whether some sort of labeling might be sufficient.

Dr. Flegal voted "no". She stated that, in our current state of knowledge, this exposes people to excess risk. She expressed concern that we don't know whether a drug-induced MTC would be as indolent as a naturally-occurring MTC. She also expressed concerns about other risks of continued monitoring. She stated that one would also have to consider the remainder of the risk:benefit context.

Dr. Teerlink expressed concern about "collateral damage" from screening and related surgeries. He stated "a couple recurrent laryngeal nerve damage, a little MRSA infection in the neck, etc, etc, by the time you start adding those up the control of blood glucose may not be balanced by all those other events".

Dr. Savage voted "no". He stated that he did not think there were enough data to be reasonably confident of the safety in humans for longterm use. He also expressed concern that it had been mentioned that this class of drugs could be particularly useful in young diabetic patients, but those would be the patients who would be most likely to have a serious consequence if they were on one of these drugs for a longer period of time. He stated that this drug was not the only way to get blood sugar under pretty good control, that there is a whole armamentarium of drugs now, and that he had not heard enough about unique advantages of adding this drug to feel confident. He expressed concern that, although the actual risk of cancer may be relatively low, the greatest risk may be "being entered into the American medical care system being screened for this sort of thing and that's something that would be out of our control, once it was out on the market".

Dr. Lesar voted "no". He was concerned about the unknown nature of the risk, and about risks associated with screening. However, he stated that he did not believe the data very strongly support that there's a high risk to the drug.

Thyroid Question 3. Assuming the remainder of the risk:benefit data are acceptable, do the available data on papillary thyroid cancer permit marketing of liraglutide?

Vote: 12 "yes", zero "no", 1 "abstain"

In general, members stated that it appeared that these small papillary thyroid carcinomata are common in the population, and that they were likely to have been incidental findings at surgery prompted by the routine calcitonin screening done in the development program. Dr. Tuttle pointed out that postmarketing screening for medullary thyroid cancer via ultrasound and neck examination could also pick up these cancers.

In addition to the public Advisory Committee meeting, the Agency had an internal Regulatory Briefing (26 Jun 2009) regarding the thyroid cancer and calcitonin data. Regulatory Briefings are internal meetings, and information from them is not releasable under the Freedom of Information Act. Data regarding thyroid cancer and calcitonin, and some efficacy data, were presented to Dr. Jenkins, the Director of the Office of New Drugs, and other senior members of the staff of the Center for Drug Evaluation and Research, representing various review disciplines. A clear consensus was not reached among panel members regarding approvability. Some panel members felt that a path to approvability was possible with the applicant's proposed postmarketing study program. In general, however, those who felt approval was possible did not concur with the applicant's assertion that monitoring of calcitonin in the clinical setting is not necessary. Other panel members were concerned about the preclinical findings and felt further premarketing study was appropriate. A formal vote regarding approvability did not occur.

8.6 Literature Review

The clinical safety reviewer consulted the medical literature for multiple areas of the review, and citations within the text refer the reader to the References section at the end of the document. In addition, on 16 Jul 2009, the clinical safety reviewer conducted a general literature search in PubMed, using the word "liraglutide", in order to search for safety concerns that might appear in

literature references, but not in submitted materials. It appeared that published safety concerns had already been addressed within the review.

8.7 Postmarketing Risk Management Plan

In a meeting with the Division on 1 Jun 2009, Novo made proposals regarding postmarketing risk management for potential risks of medullary thyroid cancer, pancreatitis, overall malignancies, and cardiovascular events. The proposal included:

- A Risk Evaluation and Mitigation Strategy (REMS), consisting of a Medication Guide
- A cardiovascular outcomes study, which would also include periodic calcitonin monitoring. b(4)
- A case series registry using North American cancer registry data. Patients who are reported to have thyroid cancer would be contacted for further information.
- An epidemiologic study using the i3 Aperio claims database. Initiators of liraglutide would be compared to matched initiators of exenatide and other diabetes drug classes, for 3-5 years.

On 8 Jul 2009, Novo submitted draft protocols for the above proposed studies. Brief synopses follow.

Cardiovascular Outcomes Study:

- Number of Subjects: 9000 patients with type 2 diabetes and increased cardiovascular risk
- Duration: minimum post-randomization followup 42 months; maximum 60 months
- Control: blinded placebo
- Background diabetes treatment: at baseline, on 0-2 oral antidiabetes medications
- Cardiovascular risk enrichment inclusion criteria: Age ≥50 years and at least one type of evidence of clinical vascular disease (prior MI; prior stroke; prior revascularization; >50% stenosis of coronary, carotid or lower extremity artery; history of angina with documented ischemia on exercise stress test or cardiac imaging; unstable angina with ECG changes or cardiac enzyme elevation; chronic heart failure of New York Heart Association Functional Class II-III). If age ≥60 years, can enter with lesser criteria of cardiovascular risk (microalbuminuria or proteinuria, hypertension with left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction by imaging, ankle:brachial index <0.9).
- Key exclusion criteria: prior insulin therapy, use of another GLP-1 based therapy, acute coronary or cerebrovascular event within 14 days prior to screening, current dialysis, prior kidney transplant or awaiting kidney transplant, prior heart transplant or awaiting heart transplant, current malignant neoplasm
- Primary endpoint: first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke
- Other endpoints of note: all-cause mortality, other major adverse cardiovascular event composites and individual components, composites including microvascular events, adverse events of special interest (pancreatitis, neoplasms, thyroid-related events, hypoglycemia), and laboratory of special interest (calcitonin, amylase, lipase)

- Patients are to continue to be followed for outcomes and adverse events, even if they discontinue study medication.
- Calcitonin screening: Measurements at BL, 3 mo, 12 mo, 24 mo, 36 mo, 48 mo and end of treatment. Study is to have independent Calcitonin Monitoring Committee. For values >100 ng/L, the patient will be referred to an independent panel of thyroid experts, will undergo a thyroid diagnostic evaluation and will likely have thyroid surgery. For values >50 and <100 ng/L, the patient will be referred to the independent panel of thyroid experts, will have a diagnostic evaluation, and may be referred for surgery if the test results indicate a need. For values ≥20 and <50 ng/L, the value will be repeated; if >50 ng/L, the patient will be evaluated as in the >50 ng/L group. For values >10 and ≤ 20 ng/L, patients will be evaluated for other factors that might increase calcitonin (e.g. histamine-2 blockers, proton pump inhibitors, pernicious anemia, smoking, autoimmune thyroiditis, heterophilic antibodies), and will have future measurements at the usual study intervals.

In general, the outline of the design of the study appears adequate to address the risk of major adverse cardiovascular events. The clinical safety reviewer recommends that the study also include systematic collection of data on immune system events. As discussed earlier, the clinical safety reviewer recommends that the first 3 years of this study be conducted prior to resubmission of a marketing application, and recommends inclusion of additional potential biomarkers for medullary thyroid carcinoma (e.g. procalcitonin and CEA).

Epidemiologic Study:

- Database: i3 Aperio claims database
- Number of subjects: all liraglutide initiators who can be matched
- Duration: 5 yrs
- Key inclusion criteria: initiators of liraglutide will undergo matching with initiators of other diabetes drugs (exenatide, sitagliptin, rosiglitazone [RSG] or pioglitazone [PIO], MET, sulfonylurea [SU])
- Elements of propensity score matching: gender, age by decades of life, U.S. geographic region, healthcare costs, # ICD codes, # drug classes dispensed, # physician visits, # ER visits, # inpatient hospital days, # laboratory tests, # procedures
- Key exclusion criteria: <6 months of health plan coverage prior to study (rationale is to allow sufficient time to evaluate baseline medical conditions)
- Primary endpoint: thyroid cancer (cell type not specified)
- Other endpoints of note: serious hypoglycemia, pancreatitis, macrovascular complications (MI, ischemic heart disease, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), other surgeries, lower limb amputation, stroke, heart failure), microvascular conditions (blindness, retinopathy, nephropathy, neuropathy, peripheral vascular disease), thyroid events

The clinical safety reviewer recommends that baseline matching occur for evidence of renal dysfunction, as declining renal function (particularly end-stage renal disease) is associated with a marked increase in cardiovascular risk.

Dr. Allen Brinker of the Office of Surveillance and Epidemiology is conducting an Epidemiology review of this proposed study. If liraglutide is approved, this proposed study could provide some additional information regarding the specified endpoints, although not of the same quality as could be obtained from a large randomized controlled prospective clinical trial.

Medullary thyroid cancer case series registry:

- Registry data sources: North American cancer registries that have an average of at least 10 reported cases of medullary thyroid cancer per year
- Identification of patients: Registries will be asked to identify all reported cases of medullary thyroid cancer.
- Contact of patients: In registries where direct patient contact is possible, the registry will send a written invitation to the patient to participate in the case series registry, and then call the patient to ask for their consent to provide their name to the Study Coordinating Center.
- Information to be obtained from patients: demographics, risk factors, comorbid conditions
- In registries where direct patient contact is not permitted, the diagnosing physician will be asked to provide the information or recruit the patient for the registry
- Other information to be obtained if possible: cancer morphology, date of diagnosis, age at diagnosis, extent of spread outside the thyroid, first course of treatment, primary surgical procedure, chemotherapy, date of last contact, vital status, family history of cancer or MEN, results of RET proto-oncogene testing, diabetes medication exposure, other medication exposure, events leading to diagnosis (e.g. calcitonin screening, thyroid nodule, thyroid ultrasound, thyroid scan, FNA, surveillance related to family history), history of radiation exposure, smoking and alcohol history
- Reporting: annual out to 10 years

Registry data can provide some information, if the participating registries actually pick up and report cases of the cancer of interest. A previous registry intended to address a potential risk of osteosarcoma associated with Forteo® was not successful in picking up the event of interest. The Office of Surveillance and Epidemiology is reviewing the proposed registry for liraglutide, with the intention of improving the likelihood that it could be an effective risk management tool.

In their proposed Risk Management Plan submitted on 8 Jul 2009, the applicant states that they will not engage in direct-to-consumer marketing (serial pg 444).

The proposed Medication Guide is reviewed in Section 9.4.2.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Subsections follow which summarize safety concerns regarding liraglutide.

9.1.1 Animal Risk of Thyroid C-Cell Tumors, and Inadequate Data to Assess the Human Risk of Medullary Thyroid Carcinoma

In two-year lifetime carcinogenicity studies of mice and rats, liraglutide caused C-cell tumors in both species, in both genders, at clinically relevant exposures. In rats, C-cell carcinomas occurred more frequently among liraglutide-treated animals, in both genders, at clinically relevant exposures. In mice, carcinomas occurred only in females and only at high multiples of expected human exposure. In rodents, C-cell adenomas (which occurred in both species at clinically relevant exposures), are considered to be precancerous lesions. A similar animal signal is being noted in interim carcinogenicity data for some other long-acting GLP-1 analogues. In animal studies, calcitonin (which has historically been used as a clinical marker for C-cell carcinomas in humans) may not have been a reliable biomarker for C-cell tumor risk. In normal rats, C-cell tumors are a common finding, but they are rare in normal mice. Calcitonin physiology differs somewhat between rodents and humans, with a more prominent role of calcitonin in overall calcium homeostasis. Also, rodent thyroids may be more likely than human thyroids to contain GLP-1 receptors.

Medullary thyroid carcinoma is the human form of C-cell cancer. It is ordinarily a rare tumor, with an incidence of about 600 cases per year in the United States. It occurs in sporadic and familial forms. It has an association with a variety of mutations in the "rearranged during transfection", or RET proto-oncogene. These mutations are found in most patients who have familial forms of the disease; the reported incidence of RET mutations among sporadic cases varies, but may be as high as 40-50%. Most cases of familial forms are diagnosed through RET screening of family members of affected probands. Most sporadic cases present as neck masses, and are diagnosed via fine needle aspiration, or are sometimes a surprise finding on surgical pathology after a thyroidectomy for a nodule that was thought preoperatively to be a differentiated thyroid cancer rather than a medullary thyroid cancer.

Medullary thyroid cancers often secrete calcitonin in excess, and therefore calcitonin can be a clinical marker. In the U.S., clinical guidelines do not recommend calcitonin screening of thyroid nodules, but some European guidelines do. C-cell hyperplasia may precede the development of medullary thyroid cancer in humans, but there is controversy regarding the predictive value of this finding.

Although usually indolent in rate of growth, the tumor can be aggressively invasive if not discovered in time for complete resection, and medullary thyroid cancer is considered to be a more serious form of thyroid cancer than the more common differentiated thyroid cancers. Early complete surgical excision is currently the only curative treatment option. Those who undergo

complete resection usually survive, and go on to die of something other than MTC. However, the outcome for nonresectable cases is much worse, with a median survival of 3.2 years, and with MTC as the cause of death among most unresectable cases. In these patients, local neck invasion, with asphyxia or other catastrophic local invasive process, is often the cause of death.

In the liraglutide program, there was one case of medullary thyroid cancer reported in a comparator-treated 61 year old man who probably had MTC at baseline, because his baseline calcitonin value was 1023 ng/L (ULN for males 8.4).

C-cell hyperplasia was noted in 5 patients treated with liraglutide, and 1 patient treated with comparator (approximate rates per 1000 patient-years of 1.7 [5 cases/2882 PY] and 0.7 [1 case/1486 PY], respectively.). The pathologic classification of C-cell hyperplasia (CCH) is an area of controversy within the pathology and endocrine communities. For a surgical finding of C-cell hyperplasia (in a patient without known familial MTC), the predictive value for the future development of MTC is unknown. The prevalence of CCH in otherwise normal thyroids is unknown; one small autopsy study suggested an incidence of up to 15% for women and 40% for men. In general, focal or nodular hyperplastic structure is considered more likely to be preneoplastic than is a diffuse pattern of hyperplasia, but some feel the distinction between the two patterns is not clinically useful.

For liraglutide-treated patients, there was one case of "neoplastic" C-cell hyperplasia, often referred to as "medullary carcinoma *in situ*" and one recently reported case of "focal" C-cell hyperplasia. More information is pending for the "focal" case, but, as noted above, a focal pattern is often felt to be a preneoplastic lesion. There were also three cases of diffuse C-cell hyperplasia among liraglutide-treated patients. Among comparator-treated patients, there was one case of "MTC *in situ*", and no other cases of C-cell hyperplasia. All cases of C-cell hyperplasia were found after protocol-specified calcitonin screening led to thyroidectomy.

Calcitonin is a peptide hormone which is synthesized primarily by the C-cells of the thyroid. It has an inhibitory effect on osteoclast-mediated bone resorption. There are multiple stimuli for release, including calcium, several gut hormones, several drugs such as proton pump inhibitors, and several disease states such as renal impairment. Historically (prior to the development of RET mutation assays), it served as a marker for the development of MTC in patients with familial forms. However, there is controversy in the medical literature regarding its usefulness for screening, with several studies suggesting a low positive predictive value for mild elevations. Normal values for the assay used in the liraglutide development program are <5 ng/L for women and <8.4 for men. Most patients with MTC have static (unstimulated) calcitonin values of >50 ng/L.

In the LGT program, static calcitonin was measured at baseline and during the 5 longterm Phase 3 trials, which included approximately 4000 patients. Dynamic calcium stimulation testing was performed on a subpopulation from 2 trials. Neither of these testing scenarios demonstrated a liraglutide-associated risk of development of marked elevations in calcitonin. Mean values were generally near the lower limit of quantitation throughout study. There were few cases of new elevations of calcitonin to >50 ng/L, and there was no difference in the incidence between

liraglutide (n=2) and comparator (n=1). Patients who had mild baseline elevations of calcitonin did not tend to develop progressive increases in calcitonin with liraglutide treatment. At 26 weeks of study (time of measurement of primary endpoint), there were some small differences in calcitonin values which did not favor liraglutide as described below. Extension data (from two trials for approximately 500 liraglutide-treated patients) out to two years do not suggest a progressive increase in calcitonin values over time, or a difference between LGT and comparator. However, extensions were voluntary and unblinded, and the percentage of dropouts was high at two years, and somewhat different between treatment groups (LGT 50%, PBO 74%, active control 57%).

Although liraglutide was not associated with a high risk of development of marked elevations in calcitonin, it may have had some effect:

- From baseline to measurement of the primary endpoint (appr 26 wks), there was a dose-dependent trend for liraglutide-treated women to shift from below the lower limit of quantitation to within the range of quantitation.
- From baseline to 26/28 weeks, the percentage of patients with any upward shift in calcitonin (i.e., from below the lower limit of quantitation to within the range of quantitation or from within the range of quantitation to above the upper limit of the reference range) was numerically highest for patients treated with the highest dose of liraglutide (1.8 mg). The 1.8 mg dose had a higher numerical percentage of shifters than the 0.6 mg and 1.2 mg LGT dose groups, and than either active or placebo control. However, dose-dependency was not demonstrated.
- At week 12, for comparisons of all doses of liraglutide to active control, or to placebo, mean percent changes in calcitonin values were statistically significantly higher for LGT versus PBO and LGT versus active control. These statistically significant differences persisted at 26 weeks for LGT versus PBO, but not for LGT versus active comparator. At 26 weeks, there was dose dependence. However, mean values were near the lower limit of quantitation, and analyses could have been affected by how the applicant's model handled values that were <LLOQ. These analyses were considered exploratory.
- The incidence of new elevations of calcitonin to >20 ng/L was numerically higher for liraglutide (0.88%) than for comparator (0.57%), and there appeared to be a dose-related trend. However, when looking at comparator groups separately, only the 1.8 mg LGT dose group (1.39%) had an incidence higher than the active comparator group (0.76%).

The clinical significance of small changes in calcitonin in this setting is uncertain.

Most trials of liraglutide were 6 months or less in duration. Calcitonin data from voluntary unblinded extensions of two trials are available for up to two years for approximately 500 liraglutide-treated patients. In the clinical safety reviewer's opinion, this duration of observation is not adequate to assess the human risk of this tumor, which may be relatively indolent in terms of expected rate of growth, but which can have very poor outcomes in unresectable cases. The applicant's proposed labeling does not provide for monitoring with calcitonin, thyroid ultrasound, or thyroid physical examination.

Besides calcitonin, there are other potential biomarkers for medullary thyroid carcinoma, including procalcitonin and carcinoembryonic antigen.

Drugs for the treatment of type 2 diabetes have the potential to be prescribed for millions of patients, and inadequately assessed safety problems can have significant public health consequences. To address the deficiency related to inadequate assessment of human medullary thyroid cancer risk for liraglutide, the clinical safety reviewer recommends a longer duration randomized, controlled, blinded trial that would include monitoring not only of calcitonin, but of these other biomarkers, with measurements at baseline and every three to six months. The applicant has already proposed a large cardiovascular outcomes trial which would include approximately 9000 patients, and which could serve the dual purpose of obtaining information regarding thyroid cancer risk. The clinical safety reviewer recommends that, in that trial, the applicant measure these biomarkers as outlined, and perform an interim analysis of calcitonin, procalcitonin and carcinoembryonic antigen levels at three years of study. At three years of study, one would not expect to see actual cases of medullary thyroid carcinoma, but the proposed analyses of multiple biomarkers could provide a reasonable assessment of whether any degree of C-cell activation is going on. Three years is recommended because currently, there are limited data for calcitonin (and no data for other biomarkers) from voluntary unblinded extensions out to two years. These extensions had high dropout rates that differed between treatment groups. At the Advisory Committee meeting, the applicant discussed calcitonin data out to two years (ref applicant's Advisory Committee presentation slide CE-73 and pg 44 of official transcript of applicant's presentation). At that Advisory Committee meeting, Dr. Burman, the Committee Chairman and one of the two thyroid cancer experts on the Committee, recommended a longer period of observation, and measurement of additional biomarkers. If there is no evidence of C-cell activation, even over three years of study, this could provide some level of comfort that the likelihood of induction of an aggressive form of medullary thyroid cancer by liraglutide would be small. With this information in hand, the public health consequences related to medullary thyroid cancer risk for liraglutide could reasonably be expected to be relatively low.

If liraglutide is approved, the issue of screening for medullary thyroid cancer may be problematic. Concern exists that screening for medullary thyroid cancer could result in an increased rate of thyroidectomies among liraglutide-treated patients. Thyroid nodules are common in the population, with an incidence of up to 30% on ultrasound. A thyroid nodule associated with an increased calcitonin level might be more likely to go to surgery. Enhanced monitoring with calcitonin or thyroid ultrasound might result in an increased rate of thyroidectomy. Whether or not liraglutide induces thyroid cancer, it might "induce" thyroidectomies. In the liraglutide development program, there were 14 thyroidectomies among liraglutide-treated patients, and 2 among comparator-treated patients (ratio approximately 3.5:1). This is potentially important, because thyroidectomy has known anesthetic and surgical risks, such as injury of the recurrent laryngeal nerve with vocal cord paralysis, hypothyroidism and hypoparathyroidism. Patients with diabetes may be more likely to have surgical complications such as infection. The applicant does not recommend that patients who receive liraglutide have baseline or ongoing monitoring with serum calcitonin, thyroid ultrasound or physical examination of the neck in the postmarketing setting, if liraglutide is approved.

9.1.2 Major Adverse Cardiovascular Events

After submission of this NDA, the Agency issued a Guidance for the Evaluation of Cardiovascular Risk in drugs intended for the treatment of type 2 diabetes. This guidance called for design of diabetes drug development programs that would permit adequate assessment of cardiovascular risk. Development programs are to include patients at higher risk of cardiovascular events in order to elicit enough events to provide adequate statistical power to assess risk. Events are to be adjudicated, and trials are to be designed so that they may be combined with other trials for meta-analysis. In the Guidance, emphasis was placed on the upper bound of the 95% confidence interval for analyses of major adverse cardiovascular events. For new diabetes drugs, if this upper bound is >1.8, approval will not be possible, and a premarketing cardiovascular outcomes trial will be needed. If the upper bound is between 1.3 and 1.8, a postmarketing cardiovascular outcomes trial will generally be required. Because the liraglutide development program was complete prior to issuance of the Guidance, its trials were not designed to provide a large number of adjudicated major cardiovascular events, and challenges existed in the evaluation of cardiovascular events. Few events had occurred, in-stream adjudication had not occurred, and *post hoc* adjudication was not possible due to inadequate data.

The applicant and the Agency carried out several types of stratified analyses, using 3 endpoints and 2 time period populations. The 3 endpoints used were intended to capture events of cardiovascular death, nonfatal myocardial infarction or stroke. These endpoints included a "Broad MACE SMQ" endpoint, a "Narrow MACE SMQ" endpoint, and a Custom FDA Endpoint. The Broad MACE SMQ endpoint was composed of two Broad Standardized MedDRA Queries (SMQs) for myocardial infarction, and cerebrovascular accidents and cerebral hemorrhages. This endpoint was hampered by the inclusion of many nonserious events, especially events of elevated CPK in the absence of other significant cardiovascular adverse events. The Narrow MACE SMQ endpoint was composed of two Narrow MedDRA SMQs, did not include elevated CPK events, but did include several event terms which appeared unlikely to represent acute cardiovascular events. The FDA Custom endpoint was a subset of the Broad SMQ endpoint. It was developed by collaboration of 3 FDA clinical reviewers, and was intended to capture only those events that were likely to represent actual events of myocardial infarction or stroke. This is not a standard FDA endpoint. All 3 endpoints also included cardiovascular deaths.

The major challenge to the assessment of risk of major adverse cardiovascular events for liraglutide was the small number of actual major adverse cardiovascular events which occurred. For the most interpretable set of data, which included FDA Custom Endpoint events out to measurement of the primary endpoint, and all liraglutide and comparator groups, there were only 26 total events across all Phase 2 and Phase 3 trials of liraglutide.

In general, comparisons of liraglutide to total comparator (placebo + active control), point estimates were <1, favoring liraglutide, and the upper bound of the 95% confidence interval for points estimates was generally >1.3 and <1.8, although it was often near 1.8. Multiple analyses were performed, and generally were not sensitive to analysis method.

The Guidance does not require that diabetes drugs meet the upper bound requirements for subgroups. However, subgroups were examined, as an assessment of the consistency of the results for the overall comparison. For comparisons of liraglutide to active control, results were qualitatively similar to those for liraglutide versus total comparator, although there was some sensitivity to method. Comparisons of liraglutide to placebo had somewhat different results, however, with several point estimates exceeding 1 (not favoring liraglutide), and multiple analyses had upper bounds that exceeded 1.8, sometimes substantially. The sensitivity to method with respect to the upper bound of the 95% confidence interval is likely explained by very low number of events, especially in the placebo group. The observation of several point estimates that were >1 for liraglutide versus placebo is not explained by higher baseline cardiovascular risk among liraglutide-treated patients; these were stratified analyses, and baseline CV risk factors did not appear to differ between treatment groups. Analyses by baseline duration of diabetes (<10 years or ≥10 years) also showed point estimates >1, and upper bounds >1.8, for comparisons of liraglutide versus placebo, particularly when one considered patients who had had diabetes for <10 years at baseline. This was not an expected finding, as the risk of MACE is generally thought to be higher in patients with diabetes of longer duration, but very low event rates limited interpretability.

In a meeting of the Endocrine and Metabolic Drugs Advisory Committee on 2 Apr 2009, analyses of MACE were discussed. This Committee also included 2 cardiologists and a biostatistician. When asked to vote on "whether the applicant had provided appropriate evidence of cardiovascular safety to conclude that liraglutide rules out unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8", the overall Committee voted 8 "yes" and 5 "no". Of note, both cardiologists and the biostatistician voted "no". These 3 members, and several of the other members (both "yes" and "no" voters) expressed concerns about the small number of events and the low cardiovascular risk of the studied population. Some expressed concerns about the differing results for analyses versus total comparator and those versus placebo. Some expressed concern about holding the applicant to a standard that was not put in place until after the development program was complete.

9.1.3 Numerical Imbalance in Cases of Papillary Thyroid Cancer

In clinical trials of liraglutide, there have been six cases of papillary thyroid cancer among liraglutide-treated patients, and one among comparator-treated patients (ratio 3:1). Most of these papillary cancers were <1 cm and were found in patients whose surgery was prompted by routine protocol-specified calcitonin or ultrasound screening. Given their small size, it is likely that these are incidental papillary microcarcinomata. However, the numerical balance in cases may not be fully explained by ascertainment "bias", as both liraglutide and placebo group patients were screened, and one would expect equal rates of incidental discovery of papillary microcarcinomata among treatment groups.

9.1.4 Gastrointestinal Adverse Events

Gastrointestinal adverse events, especially nausea, vomiting and diarrhea, occurred at a higher rate among liraglutide-treated patients than among comparator-treated patients. This was also true for withdrawals due to adverse events. Dose-dependency was noted. Gastrointestinal events occurred with greater frequency when liraglutide was combined with metformin than when metformin was used alone.

9.1.5 Pancreatitis

Across the liraglutide development program, adverse events of pancreatitis occurred in 8 liraglutide-treated patients and 1 comparator-treated patient (ratio 4:1). One case of pancreatitis in a liraglutide-treated patient was fatal, although there were confounding elements of a colonoscopy shortly prior to the patient's death, and the fact that the pancreatitis was discovered only on autopsy after an unexplained out-of-hospital death. The comparator group patient, and four of the liraglutide group patients, had risk factors for pancreatitis, such as cholelithiasis or alcohol abuse. Pancreatitis may be a class effect for GLP-1 analogues, given recent findings with exenatide, for which final labeling language and placement are under discussion. If liraglutide is approved, a discussion of pancreatitis findings should be included in labeling, and the placement should be the same as that in the final exenatide label.

9.1.6 Serious Neoplasm Events

In completed trials at the time of NDA submission, there was a numerical imbalance in the rate of serious neoplastic events, not favoring liraglutide (8.9 versus 5.3 events per 1000 PY, LGT versus non-LGT). After removing serious, but nonmalignant, neoplasms, this rate became 7.1 versus 5.3. When one also removed papillary thyroid cases, rates became 5.4 versus 4.9 events per 1000 PY.

With the 120-day safety update, additional reports came in of 7 serious neoplastic events for liraglutide, and 1 for comparator. Updated rates for total neoplastic events were 12.3 versus 8.1, and for serious malignant neoplastic events were 10.7 versus 8.1 events per 1000 PY. Only 1 of the 7 new liraglutide events was a papillary thyroid cancer. Removal of this event changed the rate ratio to 10.3 versus 8.1 events per 1000 PY.

Given recent concerns regarding a possible epidemiologic link between insulin(s) and cancer, this imbalance is of concern, as liraglutide causes an increase in insulin levels. If liraglutide is approved, future trials should include formal evaluations of malignancy risk.

9.1.7 Serious Hypoglycemia Events

Regarding nonserious hypoglycemia, liraglutide was associated with a higher incidence than rosiglitazone, a similar incidence as glargine, and a lower incidence than glimepiride. Regarding serious hypoglycemia (defined as an episode of hypoglycemia which required the assistance of another person in order to treat the hypoglycemia), all cases in the five major Phase 3 trials occurred among liraglutide-treated patients (9 LGT versus 0 comparator). In six of nine cases, a

sulfonylurea was concomitantly administered, and in two of the cases, metformin was concomitantly administered.

It will be important for this risk to be clearly communicated, because the literature regarding GLP-1-based therapies emphasizes a low theoretical risk for hypoglycemia due to the glucose-dependent nature of stimulation of insulin secretion associated with the mechanism of action. Providers and patients should know that, despite this theoretical benefit, severe hypoglycemia can in fact occur.

It is likely that the risk of serious hypoglycemia with liraglutide is similar to that for exenatide. In preliminary results from a trial of liraglutide versus exenatide, there were 2 serious hypoglycemic events among exenatide-treated patients, and one among liraglutide-treated patients.

9.1.8 Injection Site Reactions

In humans, liraglutide injection was associated with more injection site reactions than was injected placebo or injected insulin. Liraglutide dose-dependency was noted. All withdrawals due to injection site reactions in human clinical trials were among liraglutide-treated patients. In monkeys, some injection site reactions were irreversible, and were associated with peripheral eosinophilia.

9.1.9 Antibody Formation

In Phase 3 trials of liraglutide, approximately 9-10% of liraglutide-treated patients developed anti-liraglutide antibodies. Approximately 5-6% developed antibodies that cross-reacted with native GLP-1. Approximately 1-1.5% developed antibodies which exhibited a neutralizing effect on liraglutide in an *in vitro* assay.

Among liraglutide-treated patients who developed antibodies, the most common SOC for adverse events was "Infections and Infestations", while among liraglutide-treated patients who did not develop antibodies, the most common SOC was "Gastrointestinal Disorders". The infections among antibody-positive patients were primarily of the nasopharynx and upper respiratory system. Antibody-positive patients also had a numerically higher frequency of musculoskeletal pain and of certain injection site adverse event terms. However, there were also several types of injection site adverse event terms which were reported for some antibody-negative patients and not for antibody-positive patients.

Explorations of immunogenicity MedDRA SMQs did not demonstrate an association between antibody positivity and immunogenicity events. However, liraglutide-treated patients overall (regardless of antibody status) were more likely to have events from the immunogenicity SMQs.

Antibody positivity did not appear to have an overall negative impact on efficacy by mean HbA1c. However, the three patients with the highest %B/T values (≥9%) had little change from baseline to endpoint in HbA1c (Δ HbA1c 0 to -0.2), while patients with lower antibody titres had

HbA1c changes that were typical of the mean changes in the clinical trials, or higher in a few cases. The lack of decline in HbA1c for the 3 patients with the highest titres did not appear to be associated with high cross-reactivity with native GLP-1, or with anti-liraglutide neutralizing effect. These three cases are too few to reach conclusions, but it is possible that patients who develop higher titres of anti-liraglutide antibodies may have some diminution in efficacy.

9.1.10 Adverse Events Related to Immunogenicity and other Immune System Events.

Explorations using MedDRA SMQs for immunogenicity events revealed a higher numerical frequency of immunogenicity events for liraglutide-treated patients than for comparator-treated patients (11.6 versus 4.4 events per 1000 patient-years). All events were classified as nonserious except one case of angioedema. About 40% of immunogenicity events were urticaria. Other liraglutide group events included two events each of angioedema and pharyngeal edema; single events of edema of the eye, eyelid, lip, mouth or periorbital area; and single events of anaphylactic reaction and bullous dermatitis. Little information was provided regarding the episode of anaphylaxis, but it appears that this was a wheal reaction and occurred twice in the same patient, and that liraglutide was not discontinued.

In the original NDA submission, there were 9 serious adverse events of immune system disorders among liraglutide-treated patients, and none among comparator-treated patients. Review of these cases showed that some of these events were exacerbations of pre-existing conditions (adrenal insufficiency, rheumatoid arthritis), and the remainder had inadequate data to assign causality (Crohn's disease, uveitis, cryptogenic organizing pneumonia, myositis, collagen disorder). It is not possible to rule out an exacerbating effect of liraglutide in patients who have pre-existing immune system disorders.

9.1.11 Effect of Slowing of Gastric Emptying on Pharmacokinetics of Other Drugs

Liraglutide slows gastric emptying, and delayed Tmax and lowered Cmax for atorvastatin, lisinopril, paracetamol and digoxin. The clinical significance of this effect is under discussion with the Clinical Pharmacology team.

9.1.12 Lack of a Warfarin Interaction Study

The applicant did not perform a warfarin interaction study. The other approved GLP-1 analogue, exenatide, does not have a pharmacokinetic interaction with warfarin, but has safety labeling related to postmarketing reports of possible warfarin interactions. The Clinical Pharmacology team is discussing whether a warfarin interaction study would be advisable for liraglutide.

9.1.13 Numerical Imbalance in Risk for Nonmalignant Thyroid-Related Adverse Events

At the time of NDA submission, there had been 5 serious adverse nonmalignant thyroid-related adverse events (3 goitre, 1 benign thyroid neoplasm and 1 "thyroid disorder") among liraglutide-treated patients, and none among comparator-treated patients. There were also 19 cases (serious or nonserious) of "thyroid neoplasm" for liraglutide-treated patients and 4 for comparator-treated

patients (ratio 2.4:1). Goitre was reported as an adverse event for 15 LGT-treated patients and 1 comparator-treated patient (ratio 7.5:1). Most of the thyroid neoplasms were thyroid nodules discovered after protocol-specified screening via either ultrasound or calcitonin. However, the imbalance in the incidence rate of events of thyroid neoplasm and goitre may not be explained by ascertainment alone, as this would be expected to increase the detection of events in both liraglutide and comparator groups.

9.1.14 Hepatobiliary Adverse Events

In the original NDA submission, all withdrawals due to hepatobiliary adverse events (n=5) occurred among liraglutide-treated patients. These included 2 events of cholelithiasis and 1 event each of cholecystitis, hepatic cirrhosis and "hepatic function abnormal". The case of hepatic cirrhosis was associated with death, but this patient appeared to have pre-existing hepatocellular carcinoma.

During the review cycle, an additional case of "cryptogenic cirrhosis" was reported for a liraglutide-treated patient. This patient presented with bleeding varices, but had normal transaminases during treatment. The etiology of the patient's varices was unclear, but the patient did not appear to have developed active liver dysfunction while being treated with liraglutide.

When considering all hepatobiliary adverse events (not just those associated with withdrawal from study), the incidence among liraglutide-treated patients did not appear to be higher than that among comparator-treated patients.

A higher numerical percentage of liraglutide-treated patients had bilirubin levels above the upper limit of normal than did comparator-treated patients. There was no difference between treatment groups for the incidence of transaminase elevations. No patients met the criteria for Hy's law.

9.1.15 Increase in Heart Rate

Liraglutide caused an increase in heart rate of about 2-3 beats per minute. In some trials, liraglutide was associated with slightly lower mean systolic blood pressure than was comparator. Liraglutide appeared to have no effect on diastolic blood pressure.

Adverse events related to heart rate ("heart rate increased", tachycardia, supraventricular tachycardia, sinus tachycardia or tachycardia paroxysmal), occurred slightly numerically more frequently among liraglutide-treated patients than among comparator-treated patients.

A "thorough QT study" did not show evidence of a liraglutide-associated risk of QT prolongation.

9.1.16 Inadequate Preclinical Assessment of Local Toxicity Risk

In chronic repeat dose toxicity studies in monkeys, liraglutide caused irreversible injection site reactions in monkeys, using drug formulations that were dilute compared to the proposed human clinical formulation (1/3 human concentration).

Liraglutide caused fibrosarcomas in the dorsal skin and subcutis of mice in the 2-year carcinogenicity study. The concentration of liraglutide used in this study was 1/10 that of the proposed human clinical formulation.

Dr. Parola felt that the dilute nature of the formulations used in these studies resulted in inadequate characterization of these risks.

9.1.17 Inadequate Preclinical Assessment of the Genetic Toxicity Potential of Impurities

Impurity levels in the proposed human clinical formulation are higher than those used in preclinical genetic toxicity studies. Dr. Parola recommends evaluation of the *in vitro* genetic toxicity of liraglutide impurities at impurity levels consistent with drug substance and drug product acceptance criteria.

9.1.18 Risk of Medication Errors Related to Device Design and Markings

The CMC and Device reviewers expressed concerns that the proposed pen for the 0.6 and 1.2 mg doses has the potential to result in dosing errors, due to the pen labeling. This pen was adapted from another pen which had been developed for insulin administration. The Device reviewer has recommended a Human Factors study, to assess the impact of the changes in the pen on the potential for user error.

9.1.19 Potential for Off-label Use/Abuse for Weight Loss

Liraglutide was associated with a small amount of weight loss. Potential exists for off-label use for weight loss in a non-diabetic population that would not benefit from liraglutide's glucose-lowering effects, but could still be at risk for all its adverse effects.

9.1.20 Fetal Anomalies in Animals at Expected Human Exposure

Liraglutide caused major fetal malformations in rats at 0.8x expected human exposure for the 1.8 mg dose, and in rabbits at 0.2x. Five pregnancies occurred among liraglutide-treated women. Two women terminated their pregnancies. Two out of the three who did not terminate their pregnancy had healthy babies, and the third had a miscarriage. Pregnancy Category C is recommended. Liraglutide appears in maternal rat milk; it is not known if it will appear in human milk, but use during nursing is not recommended unless strong clinical reasons exist.

9.1.21 Other Nonserious Adverse Events

Dizziness and fatigue occurred more commonly among liraglutide-treated patients than among comparator-treated patients.

9.1.22 Laboratory Data Reporting Quality Issues

During the review cycle, there were some issues with data quality regarding laboratory reporting for serum calcitonin, bilirubin and creatinine. There was a discrepancy regarding missing calcitonin values, which the applicant attributed to programming errors. Two sets of errata were submitted. During the review of bilirubin and creatinine data, the clinical safety reviewer noted that the applicant's analyses had omitted some patients who had elevated values. The applicant attributed the bilirubin data omissions to a programming error, and submitted errata. A response from the applicant regarding the creatinine elevation reporting discrepancy is pending.

9.2 Recommendation on Regulatory Action

The clinical safety reviewer does not recommend approval of liraglutide at this time, for two reasons:

- A strong signal in animals of C-cell tumors of the thyroid gland, with inadequate duration of controlled study in humans to adequately assess the human risk, and
- Inadequate data to assess the risk of major adverse cardiovascular events in humans.

In the United States, there are already 11 classes of drugs approved for glycemic control in type 2 diabetes, and one other in this class. The need for new therapies for type 2 diabetes is not so urgent that one must tolerate a significant degree of uncertainty regarding serious risk concerns.

Other safety concerns exist for liraglutide, but are not part of the basis for this recommendation.

It should be noted that this reviewer conducted only the clinical safety review, and that this recommendation is made solely on the basis of safety information. The clinical efficacy review of liraglutide is ongoing by Dr. Lisa Yanoff. It is possible that signatory authorities, after having considered efficacy information and all other available data regarding liraglutide, may reasonably decide that the drug has an acceptable risk:benefit ratio.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not applicable, as approval is not recommended. However, the applicant's proposed risk management activities are discussed in Section 8.7.

9.3.2 Required Phase 4 Commitments

Not applicable, as approval is not recommended. However, the applicant's proposed Phase 4 activities are discussed in Section 8.7.

9.3.3 Other Phase 4 Requests

Not applicable, as approval is not recommended. However, the applicant's proposed Phase 4 activities are discussed in Section 8.7.

9.4 Labeling Review

Although the clinical safety reviewer does not recommend approval of liraglutide at this time, based on animal and clinical safety concerns, she acknowledges that signatory authorities evaluate all available data, including efficacy data, and that signatory authorities may decide that the possible benefits of liraglutide outweigh the safety concerns. Therefore, a review of the applicant's proposed Full Prescribing Information and Medication Guide is contained in this section.

9.4.1 Full Prescribing Information

The proposed Full Prescribing Information (FPI) does not include a Boxed Warning. If liraglutide is approved, the clinical safety reviewer recommends one, with wording similar to the following:

"Liraglutide causes C-cell tumors of the thyroid gland in rats and mice, in both genders, at clinically relevant exposures. Human data are inadequate to determine whether liraglutide will cause thyroid C-cell cancer (medullary thyroid carcinoma) in humans. Because the human risk is unknown, it is also not known whether monitoring with serum calcitonin or thyroid ultrasound will mitigate potential human risk. Patients should be counseled regarding the increased risk of thyroid C-cell tumors in rodents, and the unknown nature of the human risk. If monitoring with serum calcitonin or thyroid ultrasound occurs, patients with abnormal findings should be referred to an endocrinologist with expertise in thyroid cancer, in order to permit accurate diagnosis, to ensure that only those patients who meet criteria for thyroid surgery undergo thyroidectomy, and to avoid unnecessary and potentially harmful thyroid surgeries."

In the Highlights section, there should be an abbreviated version of the Boxed Warning, such as:

"Liraglutide causes thyroid C-cell tumors in rats and mice. Human data are inadequate to determine whether liraglutide will cause medullary thyroid cancer in humans. It is not known if monitoring with serum calcitonin or thyroid ultrasound will mitigate potential human risk. Patients with abnormal serum calcitonin or thyroid ultrasound findings should be referred to an endocrinologist to permit accurate diagnosis and to ensure that only those patients who meet criteria for thyroid surgery undergo thyroidectomy."

In the Highlights section, under "WARNINGS AND PRECAUTIONS", the following bullets should be added:

- Data are inconclusive regarding risk of major adverse cardiovascular events.
- In clinical trials, there were more cases of pancreatitis among liraglutide-treated patients than among comparator-treated patients.

- Serious hypoglycemic events may occur, especially when liraglutide is given in combination with a sulfonylurea.

In the Highlights section, under "ADVERSE REACTIONS", the following event should be added to events which occurred in ≥5% of patients: anti-liraglutide antibody formation. A separate sentence should be added, stating "Immunogenicity-related events, including urticaria, were more common among liraglutide-treated patients than among comparator-treated patients in clinical trials."

In the Highlights section, under "DRUG INTERACTIONS", the following statement should be added: "Liraglutide slows gastric emptying, which may affect the pharmacokinetics of certain drugs." (Note: This is under discussion with the Clinical Pharmacology team.)

In Section 2.2, entitled "Dosing in Combination Therapy", the paragraph regarding combination therapy with sulfonylurea should have a sentence added at the end of the paragraph such as "Serious hypoglycemic events occurred in some patients treated with liraglutide in clinical trials; most of these patients were also taking a sulfonylurea."

In Section 4, "CONTRAINDICATIONS", the word "None" should be replaced with the statement "Liraglutide is contraindicated in patients with a known medullary thyroid carcinoma or a history of medullary thyroid carcinoma; in RET-mutation-positive relatives of patients with medullary thyroid carcinoma; and in RET-mutation-status-unknown relatives of patients with medullary thyroid carcinoma."

In Section 5, "WARNINGS AND PRECAUTIONS", the current Section 5.1 should be renumbered to 5.4, and the following change should be made to the first sentence: "Patients receiving Victoza in combination with a sulfonylurea may have an increased risk of serious hypoglycemia."

A new section 5.1 should be added, entitled "C-Cell Tumors in Rodents". Suggested wording for this section is:

"Liraglutide causes C-cell tumors of the thyroid gland in rats and mice, in both genders, at clinically relevant exposures. In rats, liraglutide caused C-cell adenomas and carcinomas in both genders at clinically relevant exposures. In mice, adenomas were seen at clinically relevant exposures, but carcinomas were seen only in females at high multiples of expected human exposure. There was a long latent period from exposure to development of C-cell tumors in rodents. Human data are inadequate to determine whether liraglutide will cause thyroid C-cell cancer (medullary thyroid carcinoma) in humans.

Human medullary thyroid carcinoma is often indolent in terms of rate of growth, and the duration of clinical trials of liraglutide may not have been long enough to detect this tumor. Although medullary thyroid carcinoma may be indolent in terms of rate of growth, and is usually cured by surgery if fully resected, unresectable cases often have serious local invasive consequences and are often fatal.

In clinical trials of liraglutide, there were no treatment-emergent cases of medullary thyroid carcinoma. There were 5 cases of C-cell hyperplasia among liraglutide-treated patients, and 1 among comparator-treated patients (ratio 2.5:1 due to 2:1 randomization).

In clinical trials of liraglutide, marked elevations in calcitonin, a potential biomarker for medullary thyroid carcinoma, were generally not observed. Patients with medullary thyroid cancer usually have calcitonin values >50 ng/L. In clinical trials of liraglutide, new elevations of serum calcitonin to >50 ng/L were seen in 2 liraglutide-treated and 1 comparator-treated patient (ratio 1:1). Mean levels of calcitonin remained near the lower limit of quantitation over the duration of the controlled, blinded portions of clinical trials. During the controlled, blinded portions of clinical trials, mean percent changes in calcitonin values were statistically significantly higher for liraglutide versus placebo and liraglutide versus active control at Week 12, and at Week 26 for liraglutide versus placebo. However, these mean percent changes were small and near the lower limit of quantitation. From baseline to 26 weeks of study, upward shifts of calcitonin occurred most commonly among patients treated with the highest approved dose of liraglutide, 1.8 mg. New elevations of serum calcitonin to above 20 ng/L occurred in 0.88% of liraglutide-treated patients and 0.57% of comparator-treated patients, with an incidence of 1.39% among patients treated with 1.8 mg/day of liraglutide. The clinical significance of small changes in calcitonin in the setting of liraglutide administration is uncertain.

Because the human risk is unknown, it is also not known whether monitoring with serum calcitonin or thyroid ultrasound will mitigate potential human risk. Patients should be counseled regarding the increased risk of thyroid C-cell tumors in rodents, and the unknown nature of the human risk. If monitoring with serum calcitonin or thyroid ultrasound occurs, patients with abnormal findings should be referred to an endocrinologist with expertise in thyroid cancer, in order to permit accurate diagnosis, to ensure that only those patients who meet criteria for thyroid surgery undergo thyroidectomy, and to avoid unnecessary and potentially harmful thyroid surgeries."

A new Section 5.2 should be entitled "Inconclusive Data Regarding Risk of Major Adverse Cardiovascular Events". The following language is suggested for this section:

"Patients with a history of significant cardiovascular events were excluded from trials of liraglutide. In clinical trials of liraglutide, the overall rate of major adverse cardiovascular events was low, and there were too few events to adequately assess the risk. However, point estimates for liraglutide versus total comparator (active control plus placebo) for the risk of a composite of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke did not exceed 1."

A new Section 5.3 should be entitled "Pancreatitis". The following language is suggested for this section:

"In clinical trials of liraglutide, there were 8 cases of pancreatitis among liraglutide-treated patients and 1 case among comparator-treated patients (ratio 4:1 due to 2:1 randomization). One of the cases in a liraglutide-treated patient was fatal, although there were confounding elements

of a colonoscopy shortly prior to the patient's death, and the fact that the pancreatitis was diagnosed at autopsy after an unexplained out-of-hospital death. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. Patients should be counseled to seek immediate medical care for severe abdominal or back pain."

Reviewer note: Once consensus is reached regarding pancreatitis labeling for exenatide, it may be useful to harmonize the wording and placement in the liraglutide and exenatide labels.

In Section 6, "ADVERSE REACTIONS", the subsection entitled "Immunogenicity" should have an additional sentence at the end. "In clinical trials of liraglutide, adverse events from a composite of events potentially related to immunogenicity occurred more commonly among liraglutide-treated patients than among comparator-treated patients. The most commonly occurring event in this composite was urticaria."

In Section 6, "ADVERSE REACTIONS", the subsection entitled "Injection Site Reactions", the second sentence currently states that injection site reactions did not lead to discontinuation. However, this is not correct, and the sentence should state that some injections site reactions led to withdrawal from study.

In Section 6, "ADVERSE REACTIONS", the subsection entitled "Pancreatitis" should be removed, as the clinical safety reviewer recommends that pancreatitis be included in "WARNINGS AND PRECAUTIONS".

In Section 6, "ADVERSE REACTIONS", a subsection entitled "Papillary Thyroid Cancer" should be added. Suggested wording for the section includes "In clinical trials of liraglutide, there were 6 cases of papillary thyroid cancer in patients treated with liraglutide, and one case in a comparator-treated patient. The actual ratio was 3:1, because about twice as many patients were randomized to liraglutide than to comparator. Most of these papillary thyroid cancers were small (<1 cm) and were incidentally discovered after protocol-specified screening with serum calcitonin or thyroid ultrasound."

In Section 12, "CLINICAL PHARMACOLOGY", subsection 12.1 "Mechanism of Action", removal of certain phrases with promotional potential is recommended. This includes removal of the phrases "and improves beta-cell function" from the second paragraph; "has been shown in vitro to be a potent agent for specific stimulation of beta-cell proliferation" and "increases ... beta cell mass" from the third paragraph. These phrases may mislead readers into thinking that liraglutide is known to improve beta cell function or increase beta cell mass in humans, which is not the case.

In Section 12, "CLINICAL PHARMACOLOGY", subsection 12.2, "Pharmacodynamics", removal of the subsection entitled "Beta-cell Function" is recommended.

In Section 12, "CLINICAL PHARMACOLOGY", subsection 12.2, "Pharmacodynamics", the paragraph entitled "Body Weight, Body Composition and Energy Intake" refers to longterm clinical studies involving subjects with elevated body weight. This appears to refer to studies

conducted under the obesity IND, for which an NDA has not been submitted. This reference should be omitted, as it is an implied claim of efficacy, and liraglutide does not have an indication for treatment of obesity.

In Section 14, "CLINICAL STUDIES", in the subsection entitled "Body Weight", there are implied claims of efficacy for significant weight reduction, which should be removed, for example, "Large weight reduction was observed with increasing BMI at baseline" and "Victoza monotherapy for 52 weeks was associated with sustained weight reduction". These should be replaced with statements regarding the mean reduction in body weight, and the percentages of patients who achieved given percent reductions in body weight.

In Section 14, "CLINICAL STUDIES", the subsection entitled "Non-alcoholic Fatty Liver Disease" should be removed because it includes an implied claim of efficacy for this condition.

In Section 14, "CLINICAL STUDIES", in the subsection entitled "Other Clinical Data", an implied claim of efficacy for reduction of the occurrence of metabolic syndrome should be removed.

In Section 14, "CLINICAL STUDIES", the subsection entitled "Patient-Reported Outcomes" should be removed. In general, the Division has held that patient-reported outcomes that do not contribute to the safe or effective use of the drug should not be included in labeling.

Section 17, "PATIENT COUNSELING INFORMATION", should refer the patient to the Medication Guide. Section 17 should include a statement that patients should be counseled regarding the increase in C-cell tumors in rodents, and the fact that the human risk of medullary carcinoma of the thyroid is unknown. Patients should also be counseled that there are inadequate data to determine the cardiovascular risk of liraglutide.

9.4.2 Proposed Medication Guide

There are several areas of the Medication Guide where language can be simplified to improve understanding for patients at a lower reading level. The Division will collaborate with the Medication Guide review team in this area.

Under "What is the most important information I should know about Victoza?", the paragraph regarding medullary thyroid cancer should be the first paragraph. The sentence "During drug studies in humans with Victoza there was no evidence of an increase in MTC" should be changed to "During drug studies in humans with Victoza there was no evidence of an increase in MTC, but these studies may not have been long enough to detect MTC".

Under "How should I use Victoza?", pictures and descriptions of how to properly use the pen injector could be helpful. Medication Guides for other products with devices (for example, the Exubera® insulin inhaler), have included such pictures and descriptions in the Medication Guide.

Under "What are the possible side effects of Victoza?", a statement should be added that it is not known whether Victoza increases the risk of heart attack or stroke. The following statement should be removed, because it contains implied claims of efficacy rather than presenting useful side effect information: "Victoza may lower your appetite, the amount of food you eat, your blood pressure if it is high, and your weight."

9.5 Comments to Applicant

Comments to the applicant will depend on whether an approval action is taken.

10 APPENDICES

10.1 Review of Individual Study Reports

Please see Dr. Yanoff's clinical efficacy review. For the safety review, pooled data from multiple studies were used.

10.2 Line-by-Line Labeling Review

See Section 9.4.

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1		VICTOZA (LIRAGLUTIDE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAREN M MAHONEY
08/06/2009

HYLTON V JOFFE
08/07/2009
Please see CDTL memo.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 20, 2009

TO: John Bishai, Ph.D. Regulatory Project Manager
Karen Mahoney, M.D. Medical Officer
Lisa Yanoff, M.D. Medical Officer
Division of Metabolic and Endocrine Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D. M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: #22-341

APPLICANT: Novo-Nordisk

DRUG: Victoza (Liraglutide)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

CONSULTATION REQUEST DATE: July 10, 2008

DIVISION ACTION GOAL DATE: May 22, 2009

PDUFA DATE: March 23, 2009

Note that the action goal date is AFTER the PDUFA date.

I. BACKGROUND:

NDA 22-341 is an application for a new molecular entity liraglutide for the indication as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analog. GLP-1 is an incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Byetta (exenatide), approved in April 2005 is the only currently marketed drug of this class. Nausea has been reported in 44% of subjects in a clinical trial and acute pancreatitis has been reported in post-market surveillance reports. A clinical concern with this product is a possible risk for thyroid cancer and elevated serum calcitonin. The goals of the inspections were assessment of safety and of the primary efficacy endpoint, glycosylated hemoglobin (HbA1c) change from baseline at Week 26. For all three sites there was enrollment of large numbers of study subjects. ——— has significant equity interest (>$50,000). b(6)

The protocols inspected were:

A. Protocol NN2211-1573 entitled "Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on Glycemic Control of Liraglutide versus Glimepiride in Type 2 Diabetes [A Fifty-Two Week (with Fifty-Two Week Open-Label Extension) Double-Blind, Multicenter, Randomized, Parallel Study to Investigate Safety and Efficacy]"

B. Protocol NN2211-1574 entitled "Liraglutide Effect and Action in Diabetes (LEAD-4): Effect on Glycemic Control of Liraglutide in Combination with Rosiglitazone plus Metformin versus Rosiglitazone plus Metformin in Type 2 Diabetes (A Twenty-Six Week Double-Blind Parallel Trial to Investigate Safety and Efficacy)"

II. RESULTS (by Site):

Name of Clinical Investigator (CI) or Sponsor, and Location	Protocol # and # of Subjects:	Inspection Date	Final Classification
CI #1 Gregory Peterson, D.O. 411 Laurel St, Suite 3275 Des Moines, IA 50314	Protocol B: # NN2211-1574	November 11 to 12, 2008	NAI
CI #2 Luis Rivera-Colon, M.D. CARR 21 S 3-2 Las Lomas, Rio Pedras Puerto Rico 00924	Protocol A: # NN2211-1573	October 23 to November 14, 2008	VAI
CI #3 Andrew Lewin, M.D. National Research Center 2010 Wilshire Blvd. Suite 302 Los Angeles, CA 90057	Protocol B: # NN2211-1574	November 19 to 21, 2008	NAI
Sponsor Novo Nordisk 100 College Road West Princeton, NJ 08540	Protocol A: # NN2211-1573 Protocol B: # NN2211-1574	December 1 to 11, 2008	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Gregory E. Peterson, D.O.
Diagnostics & Critical Care Medicine
411 Laurel Street, Suite 3275
Des Moines, Iowa 50324

   a. **What was inspected**: For Protocol # NN2211-1574 at this site 26 subjects were screened, 15 subjects were enrolled and eleven subjects completed the study. There were no deaths or SAEs reported. Four subjects on placebo discontinued due to lack of efficacy. An audit of 10 subjects' records was conducted.

   b. **General observations/commentary:** The primary efficacy endpoint data were verifiable and there was no underreporting of AEs. There were no regulatory violations.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Luis Rivera-Colon, M.D.
CARR 21 S 3-2
Las Lomas, Rio Pedras, Puerto Rico 00924

a. **What was inspected:** For Protocol # NN2211-1573 at this site 36 subjects were screened, 23 subjects were enrolled and 18 subjects completed the study. There was one SAE and no deaths reported. An audit of 23 subjects' records was conducted.

b. **General observations/commentary:** The primary efficacy endpoint data were verifiable. The following regulatory violations were noted:
   1. The serious adverse event of chest pain in subject 165011 was not reported to the IRB within the timeframe required by the IRB.
   2. The clinical investigator (CI) did not report addition or increase of concomitant medications in 3 subjects as an adverse event as required by the protocol. Specifically, prescription of Tricor to subject 165017, prescription of Neurontin 600mg to subject 165013, and prescription of Tricor and increase in Zocor to subject 165035 were not reported as adverse events.
   3. The CI did not maintain adequate records concerning disposition of the drug in several instances.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Andrew Lewin, M.D.
2010 Wilshire Blvd., Suite 302
Los Angeles, CA 90057

a. **What was inspected**: For Protocol # NN2211-1574 at this site 34 subjects were screened, 26 subjects were enrolled and 21 subjects completed the study. An audit of 34 subjects' records was conducted.

b. **General observations/commentary:** No regulatory violations were noted. No under-reporting of adverse events was detected.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Novo Nordisk, Inc.
100 College Road West
Princeton, NJ 08540

a. **What was inspected**: The inspection reviewed the following sponsor responsibilities: selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, adverse drug experience effects and reporting, data collection and handling, record retention, test article accountability, and financial disclosures for clinical investigators.

b. **General observations/commentary**: Although a Form FDA 483 was issued, review of the details indicates there were no associated regulatory violations.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection of Dr. Rivera-Colon showed regulatory violations as noted above. All other inspections did not note regulatory violations.

The studies appear to have been conducted adequately, and the data generated by the clinical sites may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, MD
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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/s/

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4/21/2009 10:51:51 AM
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4/21/2009 11:05:31 AM
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1/6/09

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22-341
Brand Name	Victoza®
Generic Name	Liraglutide
Sponsor	Novo Nordisk
Indication	As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.
Dosage Form	Solution for SC injection in a pre-filled pen
Drug Class	GLP-1 analog
Therapeutic Dosing Regimen	0.6 mg/day – 1.8 mg/day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	17.5 µg/kg once daily
Submission Number and Date	N 000, 23 May 2008
Review Division	DMEP / HFD 510

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of liraglutide (1.8 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between liraglutide (1.8 mg and 1.2 mg) and placebo were below 10 ms (2.7 ms and 0.9 ms), the threshold for regulatory concern as described in ICH E14 guidance. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and peaked at hour 2.

In this randomized, double blinded, two-period crossover, placebo-controlled trial study, 52 healthy subjects received liraglutide 1.2 mg, liraglutide 1.8 mg, placebo, and a single oral dose of moxifloxacin 400 mg (positive control). Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Liraglutide (1.8 mg and 1.2 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Liraglutide 1.8 mg	8	0.3	(-2.1, 2.7)
Liraglutide 1.2 mg	3	-1.7	(-4.3, 0.9)
Moxifloxacin 400 mg*	2	12.4	(8.9, 15.9)

*Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.6 ms.

Liraglutide 1.8 mg is an adequate representation of the expected worst case scenario exposures. For a single dose administration, the maximum tolerated dose was approximately 1.3 mg. However, higher doses were tolerated when administered in a stepwise dose increase regimen. The maximum dose of liraglutide tested is a stepwise dose escalation to 2 mg. The proposed label states, "For all patients [liraglutide] should be initiated with a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on clinical response and after at least one week the dose can be increased to 1.8 mg to achieve maximum efficacy". Hence the maximum therapeutic dose that can be expected is liraglutide 1.8 mg. There are no hepatic or renal mediated elimination pathways for liraglutide that may lead to supratherapeutic exposures as a result of impaired organ function or drug-drug interactions.

There was no relationship between the liraglutide concentrations and ΔΔQTcI.

1.2 QT Interdisciplinary Review Team's Comments

In this study the sponsor used a two-stage design with moxifloxacin administered to subjects in the second stage. This two-stage design is problematic for the following reasons:

1. The effects on the QTc can be detected more easily because the positive control is administered 1 day after the baseline. In contrast, the effects for the drug and placebo are evaluated up to 21 days after the baseline.
2. The period effect (stage 1 and stage 2) may be confounded by the treatment effect. Therefore, using the second stage which was conducted in a different way from the first stage to claim assay sensitivity in the second stage is not valid.

We do not accept two-stage designs; however, in this case, the sponsor conducted the study in 2006 shortly after the formation of the QT-IRT and did not receive our comments on the acceptability of design.

The moxifloxacin administration was not blinded and the ECG measurements were only recorded for 6 h. We usually recommend that the study procedures, including ECG assessments, are the same for all treatment groups (see ICH E14 Q&A, 2008). Nevertheless, the mean QTcI-time profile was reasonable over the 6-h observation period with mean maximum ΔΔQTcI reaching at 2 h (Figure 4) and declining by 6 h.

2 PROPOSED LABEL

The sponsor has included the following information in the proposed label under Section 12.2 (Pharmacodynamics)

> Cardiac Electrophysiology (QTc):
>
> The effect of Victoza on cardiac repolarization was tested in a QTc study. Victoza at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

Reviewer's Comment: The proposed labeling is acceptable.

3 BACKGROUND

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analog. The sponsor states that Liraglutide stimulates insulin secretion and improves beta-cell function in a glucose dependent manner. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose dependent manner. During early development liraglutide was named: NNC 90-1170, NNC 0090-0000-1170, and NN2211.

Liraglutide is intended as an adjunct to diet and exercise to achieve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is developed for once-daily administration as:

- Monotherapy
- Combination therapy with one or more oral antidiabetic drugs (metformin, sulphonylureas or a thiazolidinedione) when previous therapy does not achieve adequate glycemic control

3.1 MARKET APPROVAL STATUS

Liraglutide is not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: Non-Clinical Summary, CTD section 2.6.2

> "Effect on hERG Tail Current Recorded from Stably Transfected HEK293 Cells
>
> This safety pharmacology study was designed to investigate whether liraglutide had an effect on the tail current in HEK293 cells stably transfected with the hERG cDNA (n = four cells/group). Native GLP-1 at 1 μM was also tested in 5 cells as a comparative substance. E-4031 was used as a positive reference compound.
>
> "Tail current was measured 15 min after addition of liraglutide at 0.14, 0.29 and 1.43 μM or vehicle or native GLP-1 at 1 μM to the organ bath. Liraglutide treatment at any concentration had no statistically significant effect on hERG tail current as compared to vehicle or native GLP-1.
>
> "In conclusion, at a concentration up to and including 1.43 μM, which is approximately 55 fold the human Cmax at the MHRD at 1.8 mg when administered as a single dose, liraglutide had no significant effect on hERG tail current in HEK293 cells stably transfected with hERG cDNA.

"Effects on QT interval and MAP duration in isolated perfused rabbit hearts This safety pharmacology study was designed to investigate whether liraglutide prolonged the QT interval length and MAP duration in the isolated perfused rabbit heart (according to Langendorff), four hearts per group. The heart rate and coronary flow as well as the ECG and MAP waveforms were assessed. The hearts were perfused with increasing concentrations of liraglutide, vehicle or terfenadine, which was used as positive reference compound, in 15-min intervals.

"Neither vehicle nor liraglutide at 0.14, 0.29 and 1.43 μM caused arrhythmias or abnormalities in the ECG or MAP waveform at any concentration tested. Liraglutide and vehicle caused a comparable minor decrease in rate-corrected QT-interval length and MAP duration. The heart rate increased slightly in a dose-dependent way in hearts treated with liraglutide but remained constant throughout the observation period in the vehicle-treated hearts. The coronary flow decreased in hearts treated with vehicle and was almost constant in hearts treated liraglutide.

"In conclusion, liraglutide caused no prolongation of the QT-interval length, nor did it increase MAP duration at concentrations reaching approximately 55 fold the human Cmax at the MHRD at 1.8 mg when administered as a single dose.

"Evaluation of NNC 90-1171 on cardiovascular function in conscious Cynomolgus monkey.

This safety pharmacology study was designed to investigate whether liraglutide has an effect on arterial blood pressure, heart rate, ECG (QRS-, PQ-and QT-interval), body temperature and locomotor activity after s.c. injection of liraglutide (0.02, 0.2 and 2.0 mg/kg), vehicle or saline (control item) in conscious telemetered Cynomolgus monkey (six monkeys per group). All monkeys in each group received saline, vehicle and one of the three liraglutide doses. Cardiovascular parameters, body temperature and locomotor activity were averaged over 10 seconds (except ECG) 0.5 hours before dosing, at dosing time and 1, 3, 5, 7, 9, 12, 16 and 22 hours after dosing. In the 2 mg/kg dose group the ECG was visually inspected for changes in QRS-, PR and QT-interval and compared with the ECG during vehicle and saline in the same group of animals. Noradrenaline (norepinephrine) was used as a positive control compound.

"S.C. administration of liraglutide at any dose level had no statistically significant effect on systolic, diastolic and mean blood pressure, heart rate, ECG (QRS-, PQ- and QT-interval), body temperature and locomotor activity for up to 22 hours after dosing.

"In conclusion, up to and including 2.0 mg/kg, liraglutide had no effect on cardiovascular parameters, body temperature and locomotor activity in conscious Cynomolgus monkeys. The Cmax is assumed to be approximately 600 nmol/L based on extrapolation of Cmax in the 4 week monkey toxicology study and 24 fold higher than the human Cmax at MRHD at 1.8 mg when administered as a single dose."

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Clinical Overview (CTD Section 2.5) and Summary of Clinical safety (CTD Section 2.7.4)

"During the liraglutide clinical development program, 4211 subjects were exposed to liraglutide, 1122 subjects to placebo, and 1165 subjects to an active comparator. The majority of the subjects exposed to liraglutide had type 2 diabetes (3328 subjects (79%)) and most of these were from the long-term (therapeutic confirmatory) trials.

"Generally, in the clinical development program of liraglutide, a low percentage of subjects were reported to withdraw due to adverse events (3-6%). The percentage of subjects withdrawn due to adverse events was slightly higher for subjects treated with liraglutide than for those treated with comparators (5.9% vs. 3.0%). For liraglutide, the events leading to withdrawal were mainly gastrointestinal adverse events. In general, few subjects treated with liraglutide withdrew due to serious adverse events (0.8%).

"Adverse events of special interest for liraglutide were defined as pancreatitis, thyroid adverse events and immunogenicity. Additionally, injection site reactions, cardiovascular events and neoplasms were investigated.

"During the clinical development program for liraglutide, 8 deaths (liraglutide: 3 deaths; comparators: 3 deaths; pre-randomization: 2 deaths) were reported as of the clinical cut-off date (31 Jan 2008). All deaths were reported in long-term trials. All deaths were assessed as unlikely related to the treatment regimen, except in one case (renal cell carcinoma, Subject 698004 treated with liraglutide 1.8 mg +glimepiride + metformin). However, the investigator also reported 'underlying disease' as an alternative etiology to the renal cell carcinoma. No deaths were reported up until 21 Feb 2008 in the ongoing extension trials (Trials 1573 and 1572).

"Most serious adverse events reported in the long-term trials belonged to the system organ class of cardiac disorders, with an equal distribution of the events across treatments. This is not an unexpected finding, as type 2 diabetes is associated with cardiac disease. In the liraglutide groups, the most frequently reported events were angina pectoris, acute myocardial infarction and myocardial infarction. Rates of these events were low (<10 events per 1000 subject years of exposure) and the events were overall equally distributed between treatment groups. Clinical laboratory adverse events indicative of cardiac disease (increased C-reactive protein, PAI-1 or brain natriuretic peptide) occurred at comparable rates between treatment groups.

"ECGs (10- or 12-lead) were recorded at baseline and at end of treatment, as a minimum, in all clinical trials in the liraglutide development program. T he ECG was recorded after the subjects had rested for 5 minutes in a sitting or supine position. For intermediate-term trials, the number of changes in ECG with liraglutide and placebo treatments was comparable and the few shifts (from normal to abnormal, not clinically significant or from abnormal, not clinically

significant to normal) observed for individual subjects were not considered to be clinically significant.

"ECGs from subjects in the long-term trials were available for the Screening and End of Trial Visits. The End of Trial Visits corresponded to Week 26 for long-term Trials 1572 (main trial), 1436, 1574 and 1697, whereas it corresponded to Week 52 for long-term Trial 1573. For the 1573 and 1572 open-label extension trials, there were no ECGs planned during the trials and only data from subject withdrawals are available. Overall, a comparable number and pattern of changes in ECG was observed from baseline to Weeks 26/28 and Week 52. The percentage of subjects changing ECG evaluation categories, both to better and worse categories, during the trials was comparable between the liraglutide and comparator treatment groups for both time points. Furthermore, the percentage of subjects changing ECG evaluation category from either 'normal' or 'abnormal, not clinically significant' to 'abnormal, clinically significant' was very low in all treatment groups (≤ 6 subjects in all treatment groups)."

Reviewer's Comment: The sponsor reports that there were no clinically significant ECG changes in any trial and that cardiac AEs (including ventricular arrhythmias) occurred at the same frequency in liraglutide and the comparator groups.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of liraglutide's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report NN2211-1644 for liraglutide, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Thorough QTc Evaluation of the Effect of Liraglutide on Cardiac Repolarization in Healthy Volunteers: A Randomized, Double-blind, Placebo-controlled, Two-period Crossover Study followed by Open-label Moxifloxacin (positive control) Administration

4.2.2 Protocol Number

NN2211-1644

4.2.3 Study Dates

14 July 2006 – 21 November 2006

4.2.4 Objectives

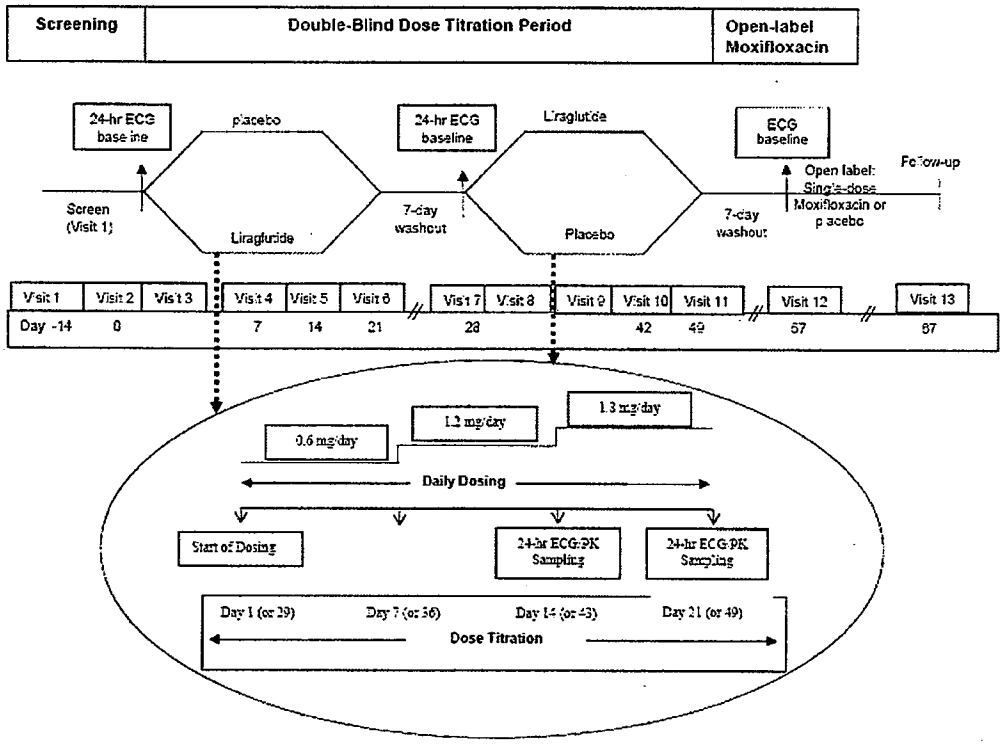
Primary objective: To assess the maximum time-matched mean difference between the baseline subtracted QTcI intervals for 1.8 mg/day liraglutide (treatment) and placebo in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, double-blind, placebo-controlled, two-period crossover design with a washout of 7 days between study periods followed by open-label moxifloxacin (positive control) administration.

Figure 2.1: Schematic of Study Design | Page: 9 of 73 |



4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Moxifloxacin was administered under open-label conditions.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

2-period crossover study:

- Placebo group
- Liraglutide treatment group:
  - 0.6 mg liraglutide daily on Days 1-7 (or crossover Days 29-35)
  - 1.2 mg daily on Days 8-14(Days 36-42)
  - 1.8 mg daily on Days 15-21(Days 43-49)

Open-label parallel study (Positive control):

- Placebo group
- Moxifloxacin group: single 400-mg dose

4.2.6.2 Sponsor's Justification for Doses

The use of a supra-therapeutic dose for liraglutide was not possible due to the following:

- There are no significant liver-mediated metabolic pathways with this drug that may lead to a supra-therapeutic exposure as a result of drug-drug interaction
- The nature of the adverse events (e.g., nausea, vomiting) and lack of experience at higher doses makes it difficult to conduct a trial to using doses higher than 1.8 mg with acceptable subject compliance and dropout rate.

For the above reasons, liraglutide was dosed at the therapeutic doses of 0.6, 1.2, and 1.8 mg.

Reviewer's Comment: The justification for using the therapeutic dose of liraglutide 1.8 mg achieved by titration with increments of 0.6 mg/day as the supratherapeutic dose is acceptable.

4.2.6.3 Instructions with Regard to Meals

Doses were administered without any regard to the timing of meals. However, the timing and the type of all meals were controlled for the visit days so as to prevent any effect on ECG.

Reviewer's Comment: Since liraglutide is administered as a subcutaneous injection, the sponsor's conduct of the study without any regard to the timing of the meals.

4.2.6.4 ECG and PK Assessments

Serial ECG determinations for time-matched baseline were performed at approximately the same time of day during Visit 2 (Day -1 – Day 0) and Visit 7 (Day 27 – 28). Post liraglutide treatment serial ECG determinations during Visit 4 (Day 14), Visit 6 (Day 21), Visit 9 (Day 42), Visit 11 (Day 49) were performed at approximately the same time of day as the pre-dose baseline readings to minimize circadian rhythm influence (±15 minutes) on QTc intervals. All subjects were rested a minimum of 15 minutes in the

supine position prior to ECG recording. The ECG readings were recorded at predose, 3, 6, 9, 9, 10, 10.5, 11, 11.512, 13, 16 and 23.5 hrs post dose. Blood samples for the assessment of the PK of liraglutide were drawn to match the timing of the ECG determination.

ECG assessments during Visit 12 (Day 57) for p.o. moxifloxacin dosing were: Baseline (six baseline ECGs collected 1 minute apart at -60, -45, -30, and -15 minutes prior to dosing), 0 hour (pre-dose) and 30, 60, and 90 minutes and 2, 4, and 6 hours after dosing. ECG recording periods preceded blood draws or other procedures to minimize artifacts. After oral moxifloxacin administration (for approximately 20 subjects randomized to moxifloxacin treatment only), blood samples (3 ml) were taken before dosing, 0 (pre-dose), 30, 60 and 90 minutes and 2, 4 and 6 hours post-dose.

Reviewer's Comment: The timing of the ECGs and plasma samples of PK assessment are acceptable. The sampling schedule assures assessment of the effect of maximum liraglutide concentration on the QT as well as any delayed effects.

4.2.6.5 Baseline

The sponsor used Day 0 time- matched QTcI values as the subject's baseline measurements for assessing changes from baseline at each post-baseline assessment time.

4.2.7 ECG Collection

Source: Protocol NN2211-1644

Serial ECG determinations were performed at the time points specified in 4.2.6.4. Care was taken that all subjects are rested a minimum of 15 minutes in the supine position prior to ECG recording.

For serial ECGs, the ECG parameters was determined manually from a minimum of 3 complexes using digitizing methods and downloaded from the ECG monitor. Lead II was preferred unless the T wave amplitude was better quantitated on other leads. ECG readings were performed using manual methods to identify the beginning and end of the QT interval for automatic recording into the ECG database. The accuracy and precision of the QT interval measurements using the selected method was described.

The QT interval was measured from the onset of the QRS complex to the end of the T wave, which is defined as the intersection of the tangent to the steepest down slope of the T wave with the isoelectric line. All ECG readings were performed by preferably one cardiologist/staff that was blinded to treatment and patient identity. ECGs from individual subjects were read by a single reviewer.

Periodically, a safety or "paper" copy ECG was printed and examined.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 58 subjects (50% males and females), 18-45 yrs of age, with a normal baseline ECG and BMI between 20-30 mg/m2 entered the crossover stage (6 subjects were randomized twice, for a total of 64 randomized), and 51 entered the parallel stage of the trial and completed all treatments. The most common reason for not completing the

study was "other". Subject 146 withdrew due to headaches and Subject 131 withdrew because she was pregnant.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor designated the QTcI as the primary QT assessment. The primary endpoint was maximum time-matched mean difference between the baseline subtracted QTcI intervals for 1.8 mg daily liraglutide and placebo.

The model was a linear mixed model with the following terms: treatment (placebo or liraglutide 1.8 mg), period (periods 1 or 2), and subjects. The factor "subjects" is a random effect factor. The other two factors are the fixed effects. The model also included the baseline QTcI as a covariate.

Table 2 presents Linear Mixed Effects Model analysis results in QTcI for liraglutide 1.8 mg/day. The upper bound of the 95% one-sided confidence interval for the time-matched maximum mean difference between QTcI for liraglutide 1.8 mg/day and placebo was below 10 ms (2.5 ms). The assay sensitivity for QTcI measurement was conducted using the moxifloxacin 400 mg as a positive control in the study, and the analysis results are presented in Table 3. The largest time-matched mean difference between QTcI for moxifloxacin and placebo was > 10 ms for QTcI (primary comparison), and occurred at 2 hours after post dosing.

Table 2: Sponsor's Mixed Model Analysis Results of QTcI for Liraglutide 1.8 mg/day

Dose (mg/day)	Type of QTc	Time Points (hrs)	Mean Delta QTc		Liraglutide-Placebo	
			Placebo N Mean (SE)	Liraglutide N Mean (SE)	Mean Difference Mean (SE)	One-Sided 95% CI (Two-Sided 90% CI) (LCL,UCL)
1.8	QTci	8.0	51 -2.4 (1.09)	51 -2.3 (1.09)	0.07 (1.47)	(-2.39, 2.53)
	QTciL	8.0	51 -2.4 (1.06)	51 -2.5 (1.06)	-0.10 (1.45)	(-2.54, 2.33)
	QTcF	8.0	51 -2.1 (1.18)	51 -3.4 (1.18)	-1.31 (1.60)	(-4.00, 1.37)
	QTcB	0.0	51 3.1 (1.84)	51 8.5 (1.84)	5.38 (1.83)	(2.29, 8.46)

Delta: The difference between QTc at current time and QTc at baseline for each patient
LCL: Lower Confidence Limit; UCL: Upper Confidence Limit

Source: Sponsor report (NN2211): Table 11.2, page 53 of 351

Table 3: Sponsor's Mixed Model Analysis Results of QTcI for Moxifloxacin

Baseline Reference	Type of QTc	Time Points (hrs)	Mean Delta QTc: Placebo N	Placebo Mean (SE)	Mean Delta QTc: Moxifloxacin N	Moxifloxacin Mean (SE)	Moxifloxacin-Placebo: Mean Difference Mean (SE)	Moxifloxacin-Placebo: One-Sided 95% CI (Two-Sided 90% CI) (LCL,UCL)
Baseline	QTci	2.0	24	-4.6 (1.54)	27	7.3 (1.46)	11.91 (2.13)	(8.35, 15.48)
	QTciL	2.0	24	-4.5 (1.50)	27	7.1 (1.41)	11.61 (2.06)	(8.16, 15.06)
	QTcF	2.0	24	-4.4 (1.39)	27	6.2 (1.31)	10.58 (1.91)	(7.37, 13.79)
	QTcB	2.0	24	-2.6 (1.92)	27	9.7 (1.81)	12.28 (2.64)	(7.85, 16.71)
Time 0	QTci	2.0	24	-2.2 (1.92)	27	11.8 (1.81)	13.95 (2.64)	(9.52, 18.39)
	QTciL	2.0	24	-2.2 (1.88)	27	11.9 (1.77)	14.09 (2.59)	(9.74, 18.43)
	QTcF	2.0	24	-2.1 (1.79)	27	11.3 (1.69)	13.38 (2.48)	(9.23, 17.54)
	QTcB	2.0	24	-4.2 (2.73)	27	11.0 (2.57)	15.27 (3.75)	(8.99, 21.55)

Delta: The difference between QTc at current time and QTc at baseline (average of time measures <0) for each patient
Delta 0: The difference between QTc at current time and QTc at Time 0 for each patient
LCL: Lower Confidence Limit UCL: Upper Confidence Limit

Source: Sponsor report (NN2211): Table 11.2, page 60 of 351

4.2.8.2.2 Categorical Analysis

The results from the categorical analyses by the sponsor were presented in Table 4. No subject's QTcI values >480 ms, and no change from baseline QTcI values >60 ms.

Table 4: Sponsor's Categorical Results

Dose*	Treatment	N	>=450 n (%) E	>=480 n (%) E	>=500 n (%) E	Increase >=30 n (%) E	Increase >=60 n (%) E
Baseline	Liraglutide	51	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0		
	Placebo	51	1 (2.0%) 1	0 (0.0%) 0	0 (0.0%) 0		
1.2	Liraglutide	50	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
	Placebo	50	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (2.0%) 1	0 (0.0%) 0
1.8	Liraglutide	51	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (2.0%) 1	0 (0.0%) 0
	Placebo	51	1 (2.0%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (3.9%) 6	0 (0.0%) 0

Source: Sponsor report (NN2211): Table 14.2.17-1, page 184 of 351

4.2.8.2.3 Additional Analyses

In addition to QTcI, the sponsor also performed analyses based on other correction methods. The results are consistent with those using QTcI.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study.

Two withdrawals occurred due to the AEs of headache and pregnancy. This pregnancy resulted in a miscarriage at approximately 8 weeks of pregnancy. The miscarriage was deemed to have an "unlikely" casual relationship to study drug.

One subject in the placebo group experienced syncope.

In the crossover phase of the trial, more subjects reported an adverse event when treated with liraglutide, as compared to placebo (62.7% vs. 38.6%). Gastrointestinal disorders and decreased appetite accounted for the difference.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for liraglutide are presented in Table 5. PK exposure following 1.2 and 1.8 mg daily sc liraglutide administration produced exposure levels similar to the results seen in prior studies using these doses. The blood samples drawn for moxifloxacin were not analyzed for PK assessment.

Table 5: Liraglutide Pharmacokinetic Parameters – Per Protocol Population

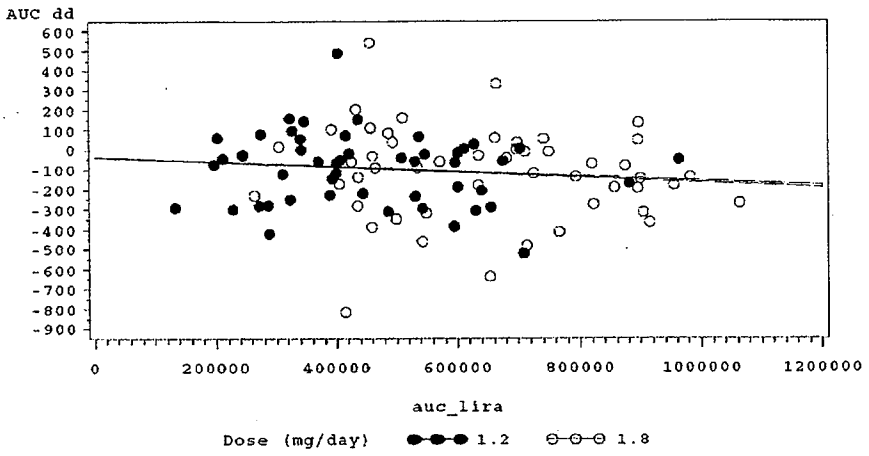
Dose (mg/day)		N	Mean	SD	Median	Min	Max
1.2	C_{max} (pmol/L)	52	26387.1	11109.97	23374.5	8015	59683
	t_{max} (hrs)	52	9.6	2.59	10.0	0	13
	AUC (pmol/L*h)	52	459934.2	182526.54	418223.1	133409	962870
1.8	C_{max} (pmol/L)	52	35806.3	11753.26	33227.5	15421	58030
	t_{max} (hrs)	52	10.1	3.73	10.0	3	24
	AUC (pmol/L*h)	52	648017.1	194718.79	663355.1	264102	1063731

Source: Table 11-10 (page 61) of sponsor's report NN2211-1644

4.2.8.4.2 Exposure-Response Analysis

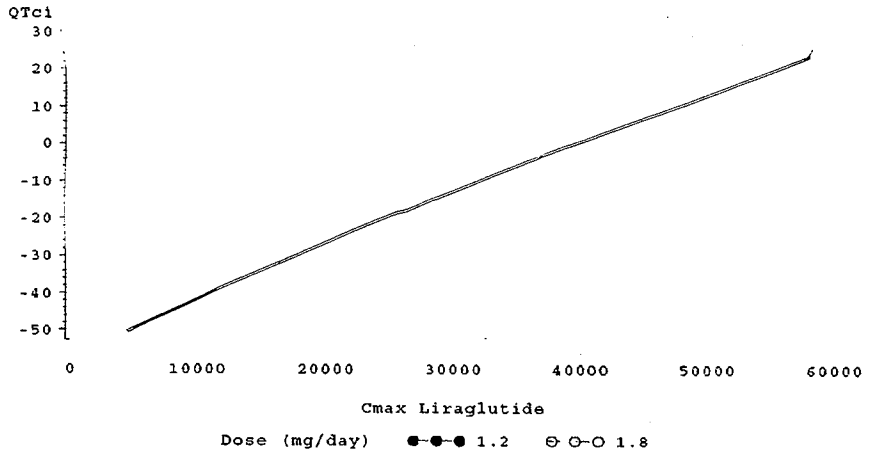
Exposure-response relationship was assessed as liraglutide AUC versus QTc effect. Plots of AUCQTc vs. drug AUC and ΔΔQTc vs. liraglutide Cmax do not show any particularly strong trend.

Figure 1: AUCQTc vs. drug AUC by Dose – Per Protocol Population



Source: Figure 11-1 (page 59) of sponsor's report NN2211-1644

Figure 2: ΔΔQTc vs. liraglutide Cmax – Per Protocol Population



b(4)

Source: Figure 11-2 (page 59) of sponsor's report NN2211-1644

Reviewer's Comments: Sponsor's graphical exploratory analysis is inadequate because of the following reasons:

- *Area under Curve (AUC) is a summary statistic and it represents the exposure and effect for the entire duration of the sampling. Given the noise in QT measurements the maximum effect on QT interval is dampened.*
- *The exploration of the relationship between liraglutide C_{max} and ΔΔQTc at C_{max} is comparatively a reasonable approach. However, this approach fails to characterize the relationship in the event of a delay between the maximum plasma concentration and the effect on QT interval. Furthermore, there is a lot of imprecision in sampling the true T_{max}.*

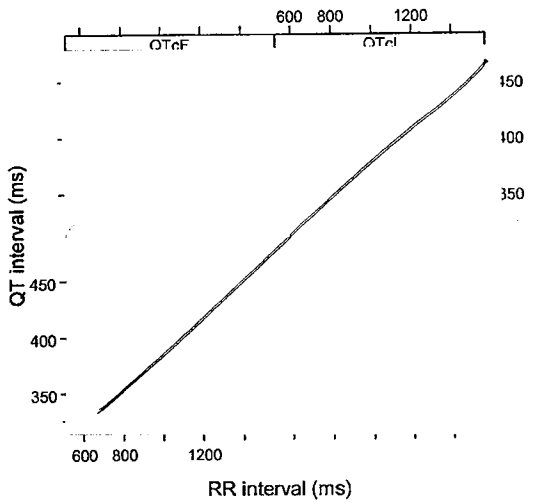
A plot of ΔΔQTc vs. drug concentrations is presented in Figure 8 *in Section 5.3 of Reviewer's Assessment.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The observed QT-RR interval relationship is presented in the following figure for different correction methods (QTcB, QTcF, QTcI) and RR.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



(4)

We used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in the following Table 6, it appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment							
	All		Liraglutide		Moxifloxacian		Placebo	
method	n	MSSS	n	MSSS	n	MSSS	n	MSSS
QTcB	64	0.0032	59	0.0035	27	0.0057	81	0.0051
QTcF	64	0.0017	59	0.0020	27	0.0014	81	0.0018
QTcI	64	0.0004	59	0.0007	27	0.0010	81	0.0012

Note: +All: Combined all treatment groups
*MSSS: Mean of Sum of Squared Slope

5.2 STATISTICAL ASSESSMENTS

The statistical reviewer used the following data set to carry out the independent analyses for statistical evaluation of the results: qtpktm.xpt in QT-IRT eRoom.

5.2.1 QTcI Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The difference of baseline-adjusted QTcI between the treatment (liraglutide 1.8 mg and 1.2 mg) and the

placebo at each time point was analyzed using PROC MIXED procedure in SAS. The model includes TREMENT, PERIOD as fixed effects and SUBJECT as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following Table 7 and

Table 8, respectively.

The largest upper bounds of the 2-sided 90% CI for the mean difference between liraglutide 1.8 mg and placebo was 2.7 ms at 8 hours after dose. (See Table 7)

The largest upper bound of the 2-sided 90% CI for the mean difference between liraglutide 1.2 mg and placebo was 0.9 ms at 3 hours after dose. (See

Table 8)

Table 7: FDA Analysis Results of ΔΔQTcI for Liraglutide 1.8 mg

	Liraglutide 1.8 mg	Placebo	ΔΔQTcI	
Time/(hr)	ΔQTcI	ΔQTcI	Diff LS Mean	90% CI
3	-3.57	0.25	-3.83	(-7.2, -0.5)
6	-3.76	0.63	-4.39	(-7.1, -1.7)
8	-2.12	-2.41	0.29	(-2.1, 2.7)
9	-3.04	0.48	-3.52	(-6.6, -0.4)
10	-3.64	0.73	-4.37	(-7.5, -1.3)
10.5	-6.92	0.18	-7.10	(-9.8, -4.4)
11	-5.49	-0.28	-5.21	(-8.4, -2.0)
11.5	-7.28	-0.92	-6.36	(-8.9, -3.8)
12	-6.97	-0.19	-6.78	(-9.7, -3.9)
13	-5.67	-0.20	-5.47	(-8.6, -2.4)
16	-3.92	-1.25	-2.67	(-5.9, 0.6)
23.5	-4.08	1.17	-5.24	(-8.4, -2.1)

Table 8: FDA Analysis Results of ΔΔQTcI for Liraglutide 1.2 mg

	Liraglutide 1.2 mg	Placebo	ΔΔQTcI	
Time/(hr)	ΔQTcI	ΔQTcI	Diff LS Mean	90% CI
3	-0.43	1.27	-1.70	(-4.3, 0.9)
6	-2.76	1.11	-3.87	(-6.4, -1.3)
8	-2.86	-0.52	-2.33	(-5.2, 0.6)
9	-2.86	1.10	-3.95	(-6.9, -1.0)
10	-2.92	1.42	-4.34	(-6.9, -1.7)
10.5	-5.37	-1.64	-3.73	(-6.2, -1.3)
11	-5.84	0.12	-5.96	(-9.0, -2.9)
11.5	-5.51	0.90	-6.41	(-9.4, -3.4)
12	-4.94	-0.09	-4.86	(-8.5, -1.2)
13	-3.62	2.21	-5.83	(-8.7, -3.0)
16	-4.18	-1.52	-2.66	(-5.5, 0.2)
23.5	-3.38	1.55	-4.93	(-7.5, -2.3)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 8.9 ms (the corresponding mean is 12.4 ms) at 2 hours after dosing, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study. After Bonferroni adjustment (adjusted by 4 time points), the largest lower confidence interval is 7.6 ms.

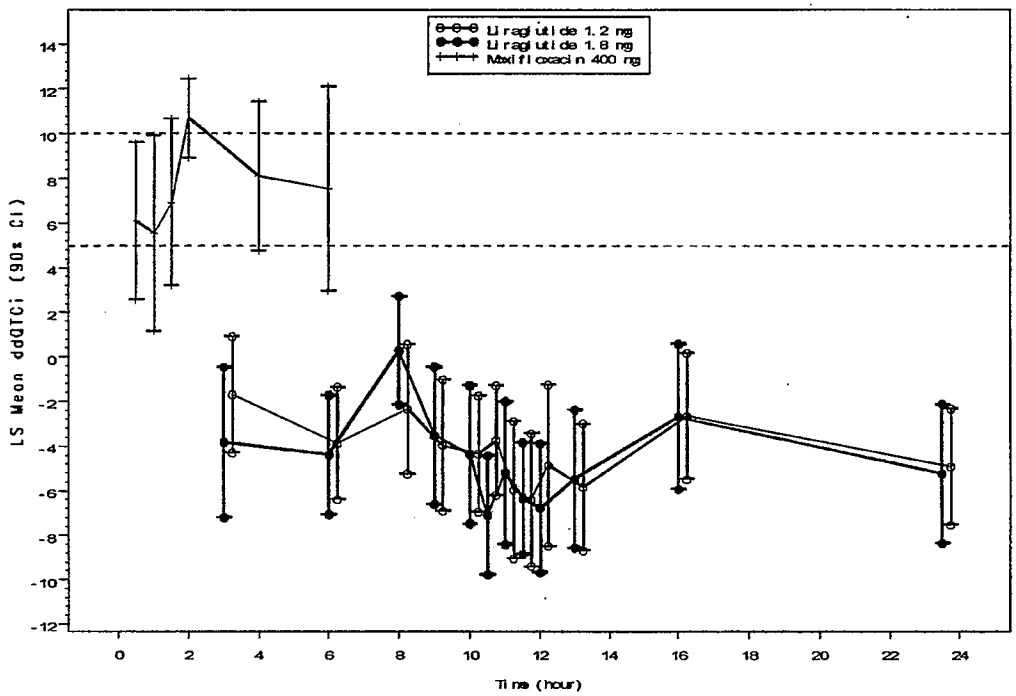
Table 9: FDA Analysis Results of ΔΔQTcI for Moxifloxacin

	Moxifloxacin	Placebo	ΔΔQTcI		
Time/(hr)	ΔQTcI	ΔQTcI	Diff LS Mean	90% CI	Adjusted* 90 % CI
0	-3.78	-1.71	-2.07	(-5.0, 0.9)	(-6.2, 2.0)
0.5	2.47	-3.60	6.07	(2.5, 9.6)	(1.2, 10.9)
1	5.29	-0.24	5.53	(1.1, 9.9)	(-0.5, 11.6)
1.5	6.02	-0.90	6.93	(3.2, 10.7)	(1.8, 12.1)
2	8.25	-4.19	12.43	(8.9, 15.9)	(7.6, 17.3)
4	-1.62	-9.72	8.10	(4.8, 11.4)	(3.5, 12.7)
6	-5.71	-13.3	7.54	(3.0, 12.1)	(1.2, 13.9)

*: Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

The following figure displays the time profile of ΔΔQTcI for different treatment groups.

Figure 4: Mean and 90% CI ΔΔQTcI Timecourse



5.2.1.3 Categorical Analysis

Categorical analyses of absolute QTcI and QTcI changes from baseline (ΔQTcI) are presented in Table 10 and Table 11, respectively. Both tables provide counts and percentages by the number of subjects as well as by the number of observations. There were no subjects whose absolute QTcI values were above 480 ms, nor were there any subjects whose ΔQTcI were above 60 ms.

Table 10: Categorical Analysis of QTcI - Liraglutide 1.8 mg/day

	Total N		Value<=450		450<Value<=480	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Liraglutide	59	2119	59 (100%)	2119 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	27	297	25 (92.6%)	289 (97.3%)	2 (7.4%)	8 (2.7%)
Placebo	57	2093	55 (96.5%)	2091 (99.9%)	2 (3.5%)	2 (0.1%)
PlaceboMx	24	264	23 (95.8%)	260 (98.5%)	1 (4.2%)	4 (1.5%)

Table 11: Categorical Analysis of ΔQTcI

	Total N		Value<=30		30<Value<=60	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Liraglutide	59	2119	58 (98.3%)	2118 (100%)	1 (1.7%)	1 (0.0%)
Moxifloxacin	27	297	27 (100%)	297 (100%)	0 (0.0%)	0 (0.0%)
Placebo	57	2093	54 (94.7%)	2086 (99.7%)	3 (5.3%)	7 (0.3%)
PlaceboMx	24	264	24 (100%)	264 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis was performed based on baseline adjusted PR intervals. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the PR mean differences between liraglutide 1.8 mg and placebo is 12.4 ms at 3 hours after dosing. Figure 5 displays the time profile of ΔΔPR.

The outlier analysis results for PR are presented in Table 13. There are 3 subjects who experienced absolute PR interval greater than 200 ms in liraglutide 1.8-mg group.

Figure 5: Mean and 90% CI ΔΔPR Timecourse

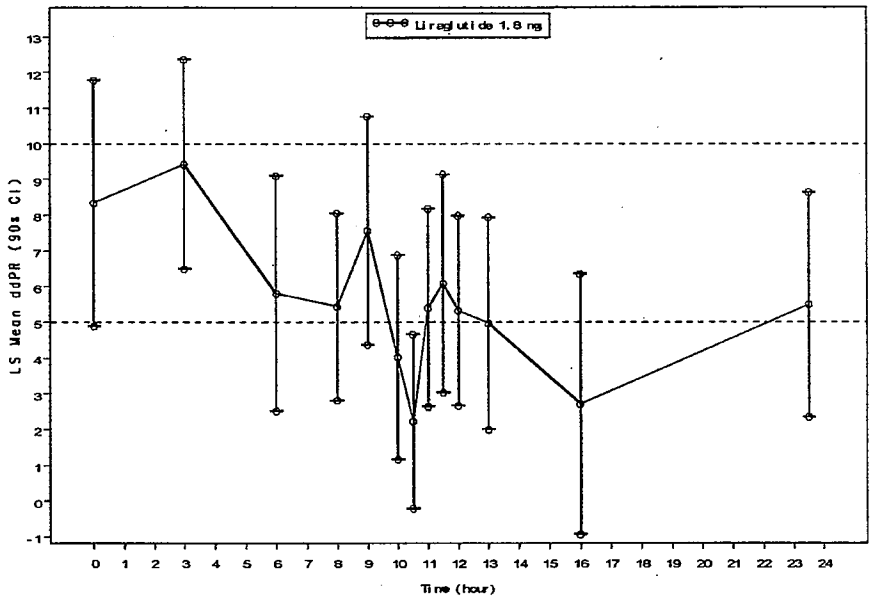


Table 12: FDA Analysis Results of ΔΔPR for Liraglutide 1.8 mg/day

	Liraglutide 1.8 mg	Placebo	ΔΔPR	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	5.58	-2.77	8.34	(4.9, 11.8)
3	7.24	-2.19	9.43	(6.5, 12.4)
6	5.59	-0.22	5.81	(2.5, 9.1)
8	4.82	-0.61	5.43	(2.8, 8.1)
9	6.88	-0.68	7.57	(4.4, 10.8)
10	3.33	-0.69	4.01	(1.2, 6.9)
10.5	2.58	0.36	2.22	(-0.2, 4.7)
11	4.83	-0.57	5.40	(2.6, 8.2)
11.5	4.63	-1.45	6.08	(3.0, 9.1)
12	3.84	-1.48	5.32	(2.7, 8.0)
13	3.75	-1.21	4.96	(2.0, 7.9)
16	2.20	-0.51	2.71	(-0.9, 6.3)
23.5	2.15	-3.34	5.49	(2.3, 8.6)

Table 13: Categorical Analysis of PR

	Total N		Value<200		Value>=200	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	59	767	54 (91.5%)	734 (95.7%)	5 (8.5%)	33 (4.3%)
Liraglutide 1.8mg	52	676	49 (94.2%)	657 (97.2%)	3 (5.8%)	19 (2.8%)

5.2.3 QRS Analysis

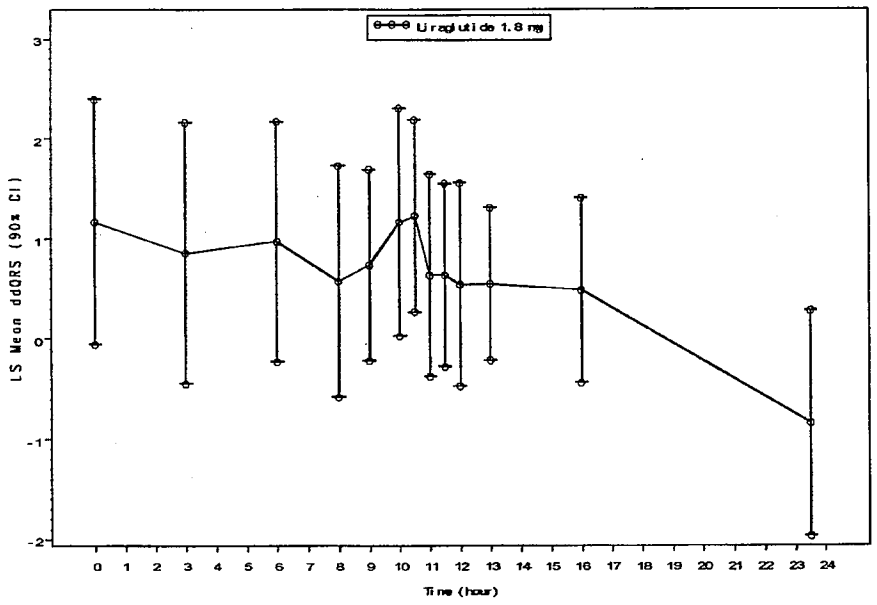
The same statistical analysis was performed based on baseline adjusted QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limit of 90% CI for the QRS mean differences between liraglutide 1.8 mg and placebo is 2.2 ms after 10.5 hours post-dosing

Table 14: FDA Analysis Results of ΔΔQRS for Liraglutide 1.8 mg/day

	Liraglutide 1.8 mg	Placebo	ΔΔQRS	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	-0.30	-1.47	1.17	(-0.1, 2.4)
3	0.31	-0.54	0.86	(-0.4, 2.2)
6	0.84	-0.13	0.97	(-0.2, 2.2)
8	0.59	0.01	0.58	(-0.6, 1.7)
9	0.06	-0.68	0.74	(-0.2, 1.7)
10	1.56	0.40	1.16	(0.0, 2.3)
10.5	0.70	-0.53	1.23	(0.3, 2.2)
11	0.73	0.10	0.63	(-0.4, 1.6)
11.5	0.51	-0.13	0.63	(-0.3, 1.5)
12	0.27	-0.27	0.54	(-0.5, 1.6)
13	0.15	-0.40	0.55	(-0.2, 1.3)
16	-0.11	-0.60	0.48	(-0.4, 1.4)
23.5	-0.71	0.13	-0.84	(-2.0, 0.3)

The following figure displays the time profile of ΔΔQRS.

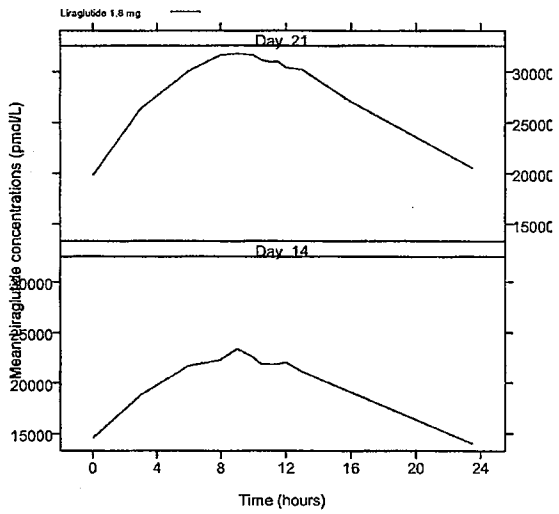
Figure 6: Mean and 90% CI ΔΔQRS Timecourse



5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

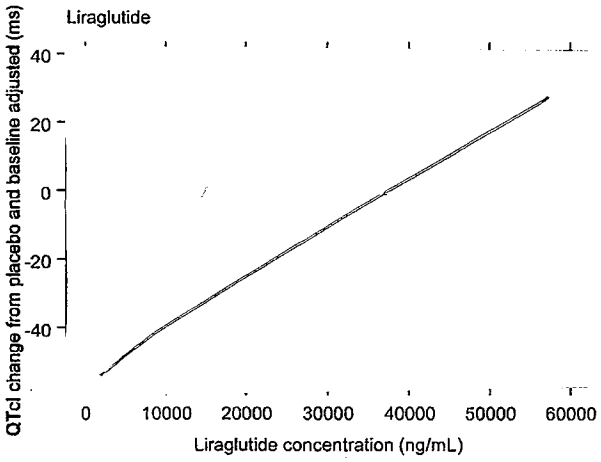
The mean drug concentration-time profile is illustrated in Figure 7.

Figure 7: Mean Liraglutide Concentration-time Profiles for Liraglutide (Day 21 Represents 1.8 mg and Day 14 Represents 1.2 mg doses Respectively)



The relationship between ΔΔQTcI and liraglutide concentrations is visualized in Figure 8 with no evident exposure-response relationship.

Figure 8: ΔΔ QTcI vs. Liraglutide Concentration



b(4)

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinicai importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study with liraglutide.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 93% of the ECGs were annotated in the primary lead II, with less than 0.1% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS intervals

Liraglutide (1.8 mg) increased the PR interval with a maximum baseline and placebo corrected difference of 9.43 ms at 3 hours (upper bound of 90% CI-12.4 ms). However this finding is not clinically relevant, since the three subjects who had an absolute PR greater than 200 ms post-treatment also had an elevated PR at baseline. For the QRS interval, the largest upper bound of the 90% CI for baseline and placebo adjusted change was 2.2 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<table>
<tr><td>Therapeutic dose</td><td colspan="2">For all patients liraglutide should be initiated with once daily doses of 0.6 mg for at least one week, after which the dose should be increased to daily doses of 1.2 mg. Based on clinical response and after at least one week the dose can be increased to 1.8 mg to achieve maximum efficacy.</td></tr>
<tr><td>Maximum tolerated dose</td><td colspan="2">For single dose administration to healthy young male subjects; the maximum tolerable dose was 17.5 µg/kg (~ mean 1.33 mg, range 1.16-1.49 mg). Higher doses are tolerated, when administered in a stepwise dose increase regimen.</td></tr>
<tr><td>Principal adverse events</td><td colspan="2">The most frequent adverse events are from the gastro intestinal organ class (nausea, diarrhea and other GI symptoms). The weekly dose increase from 0.6 mg/day to 1.2 mg/day and 1.8 mg/day is introduced to mitigate gastrointestinal symptoms.</td></tr>
<tr><td rowspan="2">Maximum dose tested</td><td>Single Dose</td><td>The maximum single dose administered in clinical pharmacology trials is 20 µg/kg (~ mean 1.44 mg (range: 1.26–1.71 mg)).</td></tr>
<tr><td>Multiple Dose</td><td>The maximum multiple daily doses administered in clinical pharmacology trials is 1.8 mg.

The maximum dose of 1.8 mg is reached by daily administrations of liraglutide 0.6 mg for one week, liraglutide 1.2 mg for one week followed by liraglutide 1.8 mg for 1-2 weeks.

(Stepwise dose escalation to liraglutide 2 mg has been administered in an early phase 2 trial, but pharmacokinetic data is not available to provide total exposure and maximum concentration).</td></tr>
<tr><td rowspan="2">Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>Single dose administration of 20 µg/kg (~ mean of 1.44 mg, range: 1.26–1.71 mg):
<table><tr><td></td><td>Mean (SD)</td><td>CV %</td></tr><tr><td>AUC pmol·h/L</td><td>523224 (104999)</td><td>19</td></tr><tr><td>Cmax pmol/L</td><td>20209 (2981)</td><td>15</td></tr></table></td></tr>
<tr><td>Multiple Dose</td><td>Multiple dose administrations of liraglutide 1.8 mg, steady state exposures:
<table><tr><td></td><td>Mean (SD)</td><td>CV %</td></tr><tr><td>AUC, pmol·h/L</td><td>809121 (186605)</td><td>23</td></tr><tr><td>Cmax pmol/L</td><td>44663 (10524)</td><td>24</td></tr></table></td></tr>
</table>

Range of linear PK	Dose proportionality was shown for AUC and C_{max} following single dose administration in the dose range 2.5 µg/kg (~ mean 0.18 mg) to 20 µg/kg (~ mean 1.44 mg). Further, dose proportionality for AUCτ for liraglutide doses of 1.2 and 1.8 mg could be assumed. An exploratory analysis of sparse sampling concentration data from an early phase 2 trial demonstrated dose proportionality across the entire dose range 0.5 – 2 mg.	
Accumulation at steady state	The mean accumulation ratio estimated on steady state liraglutide 10 µg/kg was 1.45 (SD 0.14); CV%=10. Across the dose range of 5-12.5 µg/kg, the accumulation ratio was 1.4-1.5. Based on liraglutide concentrations following a single dose of 0.6mg followed by stepwise dose increase to steady state 1.8 mg, the mean dose adjusted accumulation ratio was estimated to 1.8.	
Metabolites	Following administration of a single dose of tritium labelled liraglutide, the metabolite profiles in plasma, urine and faeces were investigated. Intact liraglutide was the major component detected in plasma: two metabolites were identified, below 5 and 9 % of total exposure in plasma. No intact liraglutide was detected in either urine or faces and only minor metabolites were present in urine and faeces (< 3% and 3-5% in urine and faeces of total radioactivity, respectively). No unique human metabolite was identified.	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability (dose 5 µg/kg): 55 % (SD 37%).
	Tmax	• Median (range) for parent Following a single dose of 20 µg/kg (~ mean 1.44 mg), tmax (median (min-max)) was: 10 h (8-12) • Median (range) for metabolites: NA, since no major metabolites have been identified
Distribution	Vd/F or Vd	Across the liraglutide doses administered, the volume of distribution ranged 11-17L. Following a single s.c. dose of 20 µg/kg (~ mean 1.44 mg), mean V_z/F was 0.14 L/kg (SD 0.02); CV%=14.
	% bound	Plasma protein binding was > 98%.
Elimination	Route	Liraglutide is metabolised similarly to native GLP-1 (i.e. by DPP-IV and NEP) but at a much slower rate. The combined in vitro and in vivo animal and human data suggest that liraglutide is fully degraded in the body with no single organ as major route of elimination.

<table>
<tr><td></td><td></td><td>• Other routes: NA</td></tr>
<tr><td></td><td>Terminal t½</td><td>Across trials, T ½ was approximately 13 h (range 9-15 h).

Following a single s.c. dose of 20 µg/kg (~ mean 1.44 mg), mean t ½ was 11 h (SD 2h); CV%=18.

• Mean (%CV) for metabolites: NA: as no major metabolites have been identified</td></tr>
<tr><td></td><td>CL/F or CL</td><td>CL/F: 0.0131 L/h/kg (CV% 31.8) (population pharmacokinetic analysis)</td></tr>
<tr><td>Intrinsic Factors</td><td>Age</td><td>Comparison of AUC_{0-t} and C_{max} for Liraglutide between elderly and young healthy subjects. No effect of age was demonstrated.
<table>
<tr><td></td><td>AUC_{0-t}
Ratio [90% CI]</td><td>C_{max}
Ratio [90% CI]</td></tr>
<tr><td>Elderly/young</td><td>0.94 [0.84; 1.06]</td><td>0.94 [0.84; 1.05]</td></tr>
</table></td></tr>
<tr><td></td><td>Sex</td><td>Comparison of AUC_{0-t} and C_{max} for Liraglutide between female and male healthy subjects.
<table>
<tr><td></td><td>AUC_{0-t}
Ratio [90% CI]</td><td>C_{max}
Ratio [90% CI]</td></tr>
<tr><td>Female/male</td><td>1.08 [0.93; 1.26]</td><td>0.96 [0.83; 1.11]</td></tr>
</table>
In contrast to the results in healthy subjects following single dose administration; a population pharmacokinetic analysis showed lower CL/F (weight adjusted) for female subjects (0.0115 L/h/kg) than for male subjects (0.0151 L/h/kg). Inter-subject variation was 29% (CV%).</td></tr>
<tr><td></td><td>Race</td><td>A population pharmacokinetic analysis investigated the effect of race on weight adjusted CL/F (i.e. exposure). In the full covariate model which also included gender effect on CL/F, the effect of race was not significant at the pre-specified significance level of 0.1% on backward elimination of the covariate.</td></tr>
<tr><td></td><td>Hepatic & Renal Impairment</td><td>Exposure was not elevated in subjects with renal or hepatic impairment compared to subjects with normal renal or hepatic function.
Comparison of $AUC_{0-\infty}$ and C_{max} for Liraglutide between Renal Groups</td></tr>
</table>

	$AUC_{0-\infty}$ Ratio [90% CI]	C_{max} Ratio [90% CI]
Mild/normal	0.67 [0.54; 0.85]	0.75 [0.57; 0.98]
Moderate/normal	0.86 [0.70; 1.07]	0.96 [0.74; 1.23]
Severe/normal	0.73 [0.57; 0.94]	0.77 [0.57; 1.03]
ESRD/normal	0.74 [0.56; 0.97]	0.92 [0.67; 1.27]

N: Normal=6; Mild=6; Moderate=7; Severe=5; ESRD=6

The statistical analysis was adjusted for effect of age and body weight

of $AUC_{0-\infty}$ and C_{max} for Liraglutide between Hepatic Groups

	$AUC_{0-\infty}$ Ratio [90% CI]	C_{max} Ratio [90% CI]
Mild/normal	0.77 [0.53; 1.11]	0.89 [0.65; 1.21]
Moderate/normal	0.87 [0.60; 1.25]	0.80 [0.59; 1.09]
Severe/normal	0.56 [0.39; 0.81]	0.71 [0.52; 0.97]

N: Normal=6; Mild=6; Moderate=6; Severe=6

The statistical analysis was adjusted for effects of age, gender and body weight.

Extrinsic Factors	Drug interactions	

Comparison of $AUC_{0-\infty}$ and C_{max} between Liraglutide (1.8 mg) and placebo for paracetamol, atorvastatin, griseofulvin, lisinopril, digoxin and ethinylestradiol / levonorgestrel

Oral Drug	Dose	N[a]	$AUC_{0-\infty}$ Ratio [90% CI]	C_{max} Ratio [90% CI]
paracetamol	1.0 g	18	1.04 [0.97; 1.10]	0.69 [0.56; 0.85]
Atorvastatin	40 mg	42	0.95 [0.89; 1.01]	0.62 [0.53; 0.72]
Griseofulvin	500 mg	22	1.10 [1.01; 1.19]	1.37 [1.24; 1.51]
Lisinopril	20 mg	40	0.85 [0.75; 0.97]	0.73 [0.63; 0.85]
Digoxin	1 mg	27	0.84 [0.72; 0.98][b]	0.69 [0.60; 0.79]
Ethinylestradiol[c]	0.03 mg	21	1.06 [0.99;1.13]	0.88 [0.79;0.97]
Levonorgestrel[c]	0.15 mg	14	1.18 [1.04;1.34][b]	0.87 [0.75;1.00]

[a] Number of subjects included in analysis of AUC

[b] Digoxin: AUC_{0-72h}, levonorgestrel: equivalence was demonstrated for AUC_{0-t} with similar ratio

		[c] Ethinylestradiol and levonorgestrel given in a combination oral contraceptive product
	Food Effects	NA
Expected High Clinical Exposure Scenario		A 65-year old male accidental took an overdose of liraglutide. On ——— ——— the subject was admitted to the hospital at 10:40 hrs due to an accidental overdose of liraglutide and symptoms of gastritis. Reportedly, the subject had administered the first dose of trial drug on 10-Sep-2006 around 10:30 hrs. Starting ———— , at 12:30 hrs the subject experienced 10-15 episodes of sweating, vomiting and abdominal discomfort. A drug count revealed that the subject accidentally administered 17.4 mg of liraglutide instead of the prescribed 10 click (0.6 mg). Examination at admission to the hospital gave the following vital sign results: blood pressure of 130/80 mm Hg, pulse rate of 90 beats/min, respiratory rate of 18/min and a blood glucose value of 114 mg/dL. ECG was found to be normal. Memory disturbances with regards to names and calculations were noted. Blood sugars, electrolytes, liver and renal functions were monitored regularly while the subject was admitted. To relieve the subject, treatment with Ondansetron, ranitidine, dextrose 10% and normal saline was commenced. The subject was discharged and considered fully recovered on ————. Liraglutide concentrations were not measured. Subject was withdrawn from the trial.

b(6)

6.2 TABLE OF STUDY ASSESSMENTS

2 Flow Chart (Trial Related Procedures)

	Screen	← Treatment (liraglutide or placebo) →					Moxifloxacin or placebo		Phone Follow-up
Visit →	Visit 1	Visit 2 & 7	Visit 3 & 8[D]	Visit 4 & 9	Visit 5 & 10[D]	Visit 6 & 11	Visit 12		Visit 13
Study Day →	-14	-1 to 1 & 27 – 29 (±3)	2 – 13 & 30 – 41 (±3)	14 & 42 (±3)	15 – 20 & 43 – 48 (±3)	21 & 49 (±3)	56 (±3)	57 (±3)	67 ± 3
Procedure↓									
1. Informed Consent/HIPPA	X								
2. Demographic info.	X								
3. Medical history/ concomitant illness	X								
4. Concomitant medication	X	X	X	X	X	X	X		X
5. Inclusion/Exclusion criteria	X								
6. Withdrawal criteria		X		X		X	X		
7. Randomization		X							
8. Complete physical exam.	X							X	
9. Targeted physical exam				X		X	X		
10. Weight	X							X	
11. Height	X								
12. Vital Signs	X			X		X		X	
13. Hematology/differential/biochemistry[E]	X							X	
14. Urinalysis	X							X	
15. Hepatitis B and C, HIV	X								
16. Urine Drug/alcohol Screen/Cotinine	X								
17. Telephone Contact									X
18. Conventional/Serial ECG	X	X[A]		X[A]		X[A]		X[A]	
20. Liraglutide/placebo/moxi dosing[B]			X	X	X	X		X	
21. PK Blood draws[C] liraglutide/moxifloxacin[C]				X		X		X	
22. Adverse Events		X	X	X	X	X	X	X	X
23. Drug accountability								X	
24. End of Trial Form									X

A. Serial ECG monitoring (as in Section 5.2.1) on days 0, 28 and 56 (for baseline QTc). On Days 14 (& 42) and 21 (& 49) serial ECG will be collected for 24 hours (6 hrs on Day 57 post moxifloxacin dosing)

B. Liraglutide daily dose (sc) – 0.6 mg on Days 1-7 (& 29-35), 1.2 mg/day on Days 8-14 (& 36-42) and 1.8 mg day on Days 15-21 (& 43-49). Single dose 400 mg moxifloxacin administered on Day 57.

C. Serial (24-hr) serum PK samples will be collected on Days 8 (& 36) and 12 (& 37) for liraglutide (optional PK samples will be collected for only 6 hours post moxifloxacin co-treatment on Day 57 – only for patients on moxifloxacin)

D. Subjects will have their daily dose administered at home by a Study nurse or in the clinic every morning at 7:00 AM (± 2 hours)

E. At baseline only serum β-hCG pregnancy test (in females)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joanne Zhang
1/5/2009 12:07:17 PM
BIOMETRICS
Dr. Park Misook was the primary statistical reviewer for this NDA.

Christine Garnett
1/5/2009 12:17:13 PM
BIOPHARMACEUTICS

Rajnikanth Madabushi
1/6/2009 09:47:23 AM
BIOPHARMACEUTICS

Suchitra Balakrishnan
1/6/2009 10:12:40 AM
MEDICAL OFFICER

Norman Stockbridge
1/6/2009 04:09:55 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22-341
Brand Name	Victoza®
Generic Name	Liraglutide
Sponsor	Novo Nordisk
Indication	As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.
Dosage Form	Solution for SC injection in a pre-filled pen
Drug Class	GLP-1 analog
Therapeutic Dosing Regimen	0.6 mg/day – 1.8 mg/day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	17.5 µg/kg once daily
Submission Number and Date	N 000, 23 May 2008
Review Division	DMEP / HFD 510

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of liraglutide (1.8 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between liraglutide (1.8 mg and 1.2 mg) and placebo were below 10 ms (2.7 ms and 0.9 ms), the threshold for regulatory concern as described in ICH E14 guidance. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and peaked at hour 2.

In this randomized, double blinded, two-period crossover, placebo-controlled trial study, 52 healthy subjects received liraglutide 1.2 mg, liraglutide 1.8 mg, placebo, and a single oral dose of moxifloxacin 400 mg (positive control). Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Liraglutide (1.8 mg and 1.2 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Liraglutide 1.8 mg	8	0.3	(-2.1, 2.7)
Liraglutide 1.2 mg	3	-1.7	(-4.3, 0.9)
Moxifloxacin 400 mg*	2	12.4	(8.9, 15.9)

*Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.6 ms.

Liraglutide 1.8 mg is an adequate representation of the expected worst case scenario exposures. For a single dose administration, the maximum tolerated dose was approximately 1.3 mg. However, higher doses were tolerated when administered in a stepwise dose increase regimen. The maximum dose of liraglutide tested is a stepwise dose escalation to 2 mg. The proposed label states, "For all patients [liraglutide] should be initiated with a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on clinical response and after at least one week the dose can be increased to 1.8 mg to achieve maximum efficacy". Hence the maximum therapeutic dose that can be expected is liraglutide 1.8 mg. There are no hepatic or renal mediated elimination pathways for liraglutide that may lead to supratherapeutic exposures as a result of impaired organ function or drug-drug interactions.

There was no relationship between the liraglutide concentrations and ΔΔQTcI.

1.2 QT Interdisciplinary Review Team's Comments

In this study the sponsor used a two-stage design with moxifloxacin administered to subjects in the second stage. This two-stage design is problematic for the following reasons:

1. The effects on the QTc can be detected more easily because the positive control is administered 1 day after the baseline. In contrast, the effects for the drug and placebo are evaluated up to 21 days after the baseline.
2. The period effect (stage 1 and stage 2) may be confounded by the treatment effect. Therefore, using the second stage which was conducted in a different way from the first stage to claim assay sensitivity in the second stage is not valid.

We do not accept two-stage designs; however, in this case, the sponsor conducted the study in 2006 shortly after the formation of the QT-IRT and did not receive our comments on the acceptability of design.

The moxifloxacin administration was not blinded and the ECG measurements were only recorded for 6 h. We usually recommend that the study procedures, including ECG assessments, are the same for all treatment groups (see ICH E14 Q&A, 2008). Nevertheless, the mean QTcI-time profile was reasonable over the 6-h observation period with mean maximum ΔΔQTcI reaching at 2 h (Figure 4) and declining by 6 h.

2 PROPOSED LABEL

The sponsor has included the following information in the proposed label under Section 12.2 (Pharmacodynamics)

> Cardiac Electrophysiology (QTc):
>
> The effect of Victoza on cardiac repolarization was tested in a QTc study. Victoza at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

Reviewer's Comment: The proposed labeling is acceptable.

3 BACKGROUND

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analog. The sponsor states that Liraglutide stimulates insulin secretion and improves beta-cell function in a glucose dependent manner. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose dependent manner. During early development liraglutide was named: NNC 90-1170, NNC 0090-0000-1170, and NN2211.

Liraglutide is intended as an adjunct to diet and exercise to achieve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is developed for once-daily administration as:

- Monotherapy
- Combination therapy with one or more oral antidiabetic drugs (metformin, sulphonylureas or a thiazolidinedione) when previous therapy does not achieve adequate glycemic control

3.1 MARKET APPROVAL STATUS

Liraglutide is not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: Non-Clinical Summary, CTD section 2.6.2

> "Effect on hERG Tail Current Recorded from Stably Transfected HEK293 Cells
>
> This safety pharmacology study was designed to investigate whether liraglutide had an effect on the tail current in HEK293 cells stably transfected with the hERG cDNA (n = four cells/group). Native GLP-1 at 1 μM was also tested in 5 cells as a comparative substance. E-4031 was used as a positive reference compound.
>
> "Tail current was measured 15 min after addition of liraglutide at 0.14, 0.29 and 1.43 μM or vehicle or native GLP-1 at 1 μM to the organ bath. Liraglutide treatment at any concentration had no statistically significant effect on hERG tail current as compared to vehicle or native GLP-1.
>
> "In conclusion, at a concentration up to and including 1.43 μM, which is approximately 55 fold the human Cmax at the MHRD at 1.8 mg when administered as a single dose, liraglutide had no significant effect on hERG tail current in HEK293 cells stably transfected with hERG cDNA.

"Effects on QT interval and MAP duration in isolated perfused rabbit hearts This safety pharmacology study was designed to investigate whether liraglutide prolonged the QT interval length and MAP duration in the isolated perfused rabbit heart (according to Langendorff), four hearts per group. The heart rate and coronary flow as well as the ECG and MAP waveforms were assessed. The hearts were perfused with increasing concentrations of liraglutide, vehicle or terfenadine, which was used as positive reference compound, in 15-min intervals.

"Neither vehicle nor liraglutide at 0.14, 0.29 and 1.43 μM caused arrhythmias or abnormalities in the ECG or MAP waveform at any concentration tested. Liraglutide and vehicle caused a comparable minor decrease in rate-corrected QT-interval length and MAP duration. The heart rate increased slightly in a dose-dependent way in hearts treated with liraglutide but remained constant throughout the observation period in the vehicle-treated hearts. The coronary flow decreased in hearts treated with vehicle and was almost constant in hearts treated liraglutide.

"In conclusion, liraglutide caused no prolongation of the QT-interval length, nor did it increase MAP duration at concentrations reaching approximately 55 fold the human Cmax at the MHRD at 1.8 mg when administered as a single dose.

"Evaluation of NNC 90-1171 on cardiovascular function in conscious Cynomolgus monkey.

This safety pharmacology study was designed to investigate whether liraglutide has an effect on arterial blood pressure, heart rate, ECG (QRS-, PQ-and QT-interval), body temperature and locomotor activity after s.c. injection of liraglutide (0.02, 0.2 and 2.0 mg/kg), vehicle or saline (control item) in conscious telemetered Cynomolgus monkey (six monkeys per group). All monkeys in each group received saline, vehicle and one of the three liraglutide doses. Cardiovascular parameters, body temperature and locomotor activity were averaged over 10 seconds (except ECG) 0.5 hours before dosing, at dosing time and 1, 3, 5, 7, 9, 12, 16 and 22 hours after dosing. In the 2 mg/kg dose group the ECG was visually inspected for changes in QRS-, PR and QT-interval and compared with the ECG during vehicle and saline in the same group of animals. Noradrenaline (norepinephrine) was used as a positive control compound.

"S.C. administration of liraglutide at any dose level had no statistically significant effect on systolic, diastolic and mean blood pressure, heart rate, ECG (QRS-, PQ- and QT-interval), body temperature and locomotor activity for up to 22 hours after dosing.

"In conclusion, up to and including 2.0 mg/kg, liraglutide had no effect on cardiovascular parameters, body temperature and locomotor activity in conscious Cynomolgus monkeys. The Cmax is assumed to be approximately 600 nmol/L based on extrapolation of Cmax in the 4 week monkey toxicology study and 24 fold higher than the human Cmax at MRHD at 1.8 mg when administered as a single dose."

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Clinical Overview (CTD Section 2.5) and Summary of Clinical safety (CTD Section 2.7.4)

"During the liraglutide clinical development program, 4211 subjects were exposed to liraglutide, 1122 subjects to placebo, and 1165 subjects to an active comparator. The majority of the subjects exposed to liraglutide had type 2 diabetes (3328 subjects (79%)) and most of these were from the long-term (therapeutic confirmatory) trials.

"Generally, in the clinical development program of liraglutide, a low percentage of subjects were reported to withdraw due to adverse events (3-6%). The percentage of subjects withdrawn due to adverse events was slightly higher for subjects treated with liraglutide than for those treated with comparators (5.9% vs. 3.0%). For liraglutide, the events leading to withdrawal were mainly gastrointestinal adverse events. In general, few subjects treated with liraglutide withdrew due to serious adverse events (0.8%).

"Adverse events of special interest for liraglutide were defined as pancreatitis, thyroid adverse events and immunogenicity. Additionally, injection site reactions, cardiovascular events and neoplasms were investigated.

"During the clinical development program for liraglutide, 8 deaths (liraglutide: 3 deaths; comparators: 3 deaths; pre-randomization: 2 deaths) were reported as of the clinical cut-off date (31 Jan 2008). All deaths were reported in long-term trials. All deaths were assessed as unlikely related to the treatment regimen, except in one case (renal cell carcinoma, Subject 698004 treated with liraglutide 1.8 mg +glimepiride + metformin). However, the investigator also reported 'underlying disease' as an alternative etiology to the renal cell carcinoma. No deaths were reported up until 21 Feb 2008 in the ongoing extension trials (Trials 1573 and 1572).

"Most serious adverse events reported in the long-term trials belonged to the system organ class of cardiac disorders, with an equal distribution of the events across treatments. This is not an unexpected finding, as type 2 diabetes is associated with cardiac disease. In the liraglutide groups, the most frequently reported events were angina pectoris, acute myocardial infarction and myocardial infarction. Rates of these events were low (<10 events per 1000 subject years of exposure) and the events were overall equally distributed between treatment groups. Clinical laboratory adverse events indicative of cardiac disease (increased C-reactive protein, PAI-1 or brain natriuretic peptide) occurred at comparable rates between treatment groups.

"ECGs (10- or 12-lead) were recorded at baseline and at end of treatment, as a minimum, in all clinical trials in the liraglutide development program. T he ECG was recorded after the subjects had rested for 5 minutes in a sitting or supine position. For intermediate-term trials, the number of changes in ECG with liraglutide and placebo treatments was comparable and the few shifts (from normal to abnormal, not clinically significant or from abnormal, not clinically

significant to normal) observed for individual subjects were not considered to be clinically significant.

"ECGs from subjects in the long-term trials were available for the Screening and End of Trial Visits. The End of Trial Visits corresponded to Week 26 for long-term Trials 1572 (main trial), 1436, 1574 and 1697, whereas it corresponded to Week 52 for long-term Trial 1573. For the 1573 and 1572 open-label extension trials, there were no ECGs planned during the trials and only data from subject withdrawals are available. Overall, a comparable number and pattern of changes in ECG was observed from baseline to Weeks 26/28 and Week 52. The percentage of subjects changing ECG evaluation categories, both to better and worse categories, during the trials was comparable between the liraglutide and comparator treatment groups for both time points. Furthermore, the percentage of subjects changing ECG evaluation category from either 'normal' or 'abnormal, not clinically significant' to 'abnormal, clinically significant' was very low in all treatment groups (≤ 6 subjects in all treatment groups)."

Reviewer's Comment: The sponsor reports that there were no clinically significant ECG changes in any trial and that cardiac AEs (including ventricular arrhythmias) occurred at the same frequency in liraglutide and the comparator groups.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of liraglutide's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report NN2211-1644 for liraglutide, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Thorough QTc Evaluation of the Effect of Liraglutide on Cardiac Repolarization in Healthy Volunteers: A Randomized, Double-blind, Placebo-controlled, Two-period Crossover Study followed by Open-label Moxifloxacin (positive control) Administration

4.2.2 Protocol Number

NN2211-1644

4.2.3 Study Dates

14 July 2006 – 21 November 2006

4.2.4 Objectives

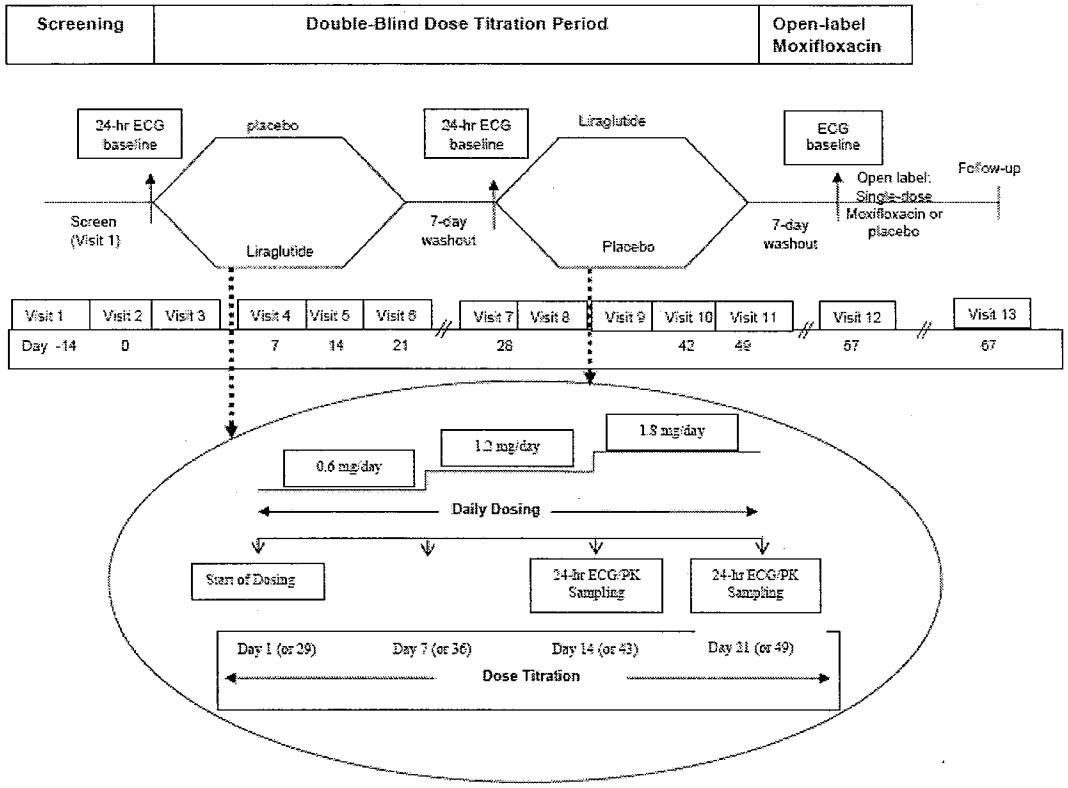
Primary objective: To assess the maximum time-matched mean difference between the baseline subtracted QTcI intervals for 1.8 mg/day liraglutide (treatment) and placebo in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, double-blind, placebo-controlled, two-period crossover design with a washout of 7 days between study periods followed by open-label moxifloxacin (positive control) administration.

Figure 2.1: Schematic of Study Design | Page: 9 of 73 |



4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Moxifloxacin was administered under open-label conditions.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

2-period crossover study:

- Placebo group
- Liraglutide treatment group:
    - 0.6 mg liraglutide daily on Days 1-7 (or crossover Days 29-35)
    - 1.2 mg daily on Days 8-14(Days 36-42)
    - 1.8 mg daily on Days 15-21(Days 43-49)

Open-label parallel study (Positive control):

- Placebo group
- Moxifloxacin group: single 400-mg dose

4.2.6.2 Sponsor's Justification for Doses

The use of a supra-therapeutic dose for liraglutide was not possible due to the following:

- There are no significant liver-mediated metabolic pathways with this drug that may lead to a supra-therapeutic exposure as a result of drug-drug interaction
- The nature of the adverse events (e.g., nausea, vomiting) and lack of experience at higher doses makes it difficult to conduct a trial to using doses higher than 1.8 mg with acceptable subject compliance and dropout rate.

For the above reasons, liraglutide was dosed at the therapeutic doses of 0.6, 1.2, and 1.8 mg.

Reviewer's Comment: The justification for using the therapeutic dose of liraglutide 1.8 mg achieved by titration with increments of 0.6 mg/day as the supratherapeutic dose is acceptable.

4.2.6.3 Instructions with Regard to Meals

Doses were administered without any regard to the timing of meals. However, the timing and the type of all meals were controlled for the visit days so as to prevent any effect on ECG.

Reviewer's Comment: Since liraglutide is administered as a subcutaneous injection, the sponsor's conduct of the study without any regard to the timing of the meals.

4.2.6.4 ECG and PK Assessments

Serial ECG determinations for time-matched baseline were performed at approximately the same time of day during Visit 2 (Day -1 – Day 0) and Visit 7 (Day 27 – 28). Post liraglutide treatment serial ECG determinations during Visit 4 (Day 14), Visit 6 (Day 21), Visit 9 (Day 42), Visit 11 (Day 49) were performed at approximately the same time of day as the pre-dose baseline readings to minimize circadian rhythm influence (±15 minutes) on QTc intervals. All subjects were rested a minimum of 15 minutes in the

supine position prior to ECG recording. The ECG readings were recorded at predose, 3, 6, 9, 9, 10, 10.5, 11, 11.512, 13, 16 and 23.5 hrs post dose. Blood samples for the assessment of the PK of liraglutide were drawn to match the timing of the ECG determination.

ECG assessments during Visit 12 (Day 57) for p.o. moxifloxacin dosing were: Baseline (six baseline ECGs collected 1 minute apart at -60, -45, -30, and -15 minutes prior to dosing), 0 hour (pre-dose) and 30, 60, and 90 minutes and 2, 4, and 6 hours after dosing. ECG recording periods preceded blood draws or other procedures to minimize artifacts. After oral moxifloxacin administration (for approximately 20 subjects randomized to moxifloxacin treatment only), blood samples (3 ml) were taken before dosing, 0 (pre-dose), 30, 60 and 90 minutes and 2, 4 and 6 hours post-dose.

Reviewer's Comment: The timing of the ECGs and plasma samples of PK assessment are acceptable. The sampling schedule assures assessment of the effect of maximum liraglutide concentration on the QT as well as any delayed effects.

4.2.6.5 Baseline

The sponsor used Day 0 time- matched QTcI values as the subject's baseline measurements for assessing changes from baseline at each post-baseline assessment time.

4.2.7 ECG Collection

Source: Protocol NN2211-1644

Serial ECG determinations were performed at the time points specified in 4.2.6.4. Care was taken that all subjects are rested a minimum of 15 minutes in the supine position prior to ECG recording.

For serial ECGs, the ECG parameters was determined manually from a minimum of 3 complexes using digitizing methods and downloaded from the ECG monitor. Lead II was preferred unless the T wave amplitude was better quantitated on other leads. ECG readings were performed using manual methods to identify the beginning and end of the QT interval for automatic recording into the ECG database. The accuracy and precision of the QT interval measurements using the selected method was described.

The QT interval was measured from the onset of the QRS complex to the end of the T wave, which is defined as the intersection of the tangent to the steepest down slope of the T wave with the isoelectric line. All ECG readings were performed by preferably one cardiologist/staff that was blinded to treatment and patient identity. ECGs from individual subjects were read by a single reviewer.

Periodically, a safety or "paper" copy ECG was printed and examined.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 58 subjects (50% males and females), 18-45 yrs of age, with a normal baseline ECG and BMI between 20-30 mg/m2 entered the crossover stage (6 subjects were randomized twice, for a total of 64 randomized), and 51 entered the parallel stage of the trial and completed all treatments. The most common reason for not completing the

study was "other". Subject 146 withdrew due to headaches and Subject 131 withdrew because she was pregnant.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor designated the QTcI as the primary QT assessment. The primary endpoint was maximum time-matched mean difference between the baseline subtracted QTcI intervals for 1.8 mg daily liraglutide and placebo.

The model was a linear mixed model with the following terms: treatment (placebo or liraglutide 1.8 mg), period (periods 1 or 2), and subjects. The factor "subjects" is a random effect factor. The other two factors are the fixed effects. The model also included the baseline QTcI as a covariate.

Table 2 presents Linear Mixed Effects Model analysis results in QTcI for liraglutide 1.8 mg/day. The upper bound of the 95% one-sided confidence interval for the time-matched maximum mean difference between QTcI for liraglutide 1.8 mg/day and placebo was below 10 ms (2.5 ms). The assay sensitivity for QTcI measurement was conducted using the moxifloxacin 400 mg as a positive control in the study, and the analysis results are presented in Table 3. The largest time-matched mean difference between QTcI for moxifloxacin and placebo was > 10 ms for QTcI (primary comparison), and occurred at 2 hours after post dosing.

Table 2: Sponsor's Mixed Model Analysis Results of QTcI for Liraglutide 1.8 mg/day

Dose (mg/day)	Type of QTc	Time Points (hrs)	Mean Delta QTc		Liraglutide-Placebo	
			Placebo N Mean (SE)	Liraglutide N Mean (SE)	Mean Difference Mean (SE)	One-Sided 95% CI (Two-Sided 90% CI) (LCL,UCL)
1.8	QTci	8.0	51 -2.4 (1.09)	51 -2.3 (1.09)	0.07 (1.47)	(-2.39, 2.53)
	QTciL	8.0	51 -2.4 (1.06)	51 -2.5 (1.06)	-0.10 (1.45)	(-2.54, 2.33)
	QTcF	8.0	51 -2.1 (1.18)	51 -3.4 (1.18)	-1.31 (1.60)	(-4.00, 1.37)
	QTcB	0.0	51 3.1 (1.84)	51 8.5 (1.84)	5.38 (1.83)	(2.29, 8.46)

Delta: The difference between QTc at current time and QTc at baseline for each patient
LCL: Lower Confidence Limit; UCL: Upper Confidence Limit

Source: Sponsor report (NN2211): Table 11.2, page 53 of 351

Table 3: Sponsor's Mixed Model Analysis Results of QTcI for Moxifloxacin

Baseline Reference	Type of QTc	Time Points (hrs)	Mean Delta QTc: Placebo N	Placebo Mean (SE)	Mean Delta QTc: Moxifloxacin N	Moxifloxacin Mean (SE)	Moxifloxacin-Placebo: Mean Difference Mean (SE)	Moxifloxacin-Placebo: One-Sided 95% CI (Two-Sided 90% CI) (LCL,UCL)
Baseline	QTci	2.0	24	-4.6 (1.54)	27	7.3 (1.46)	11.91 (2.13)	(8.35, 15.48)
	QTciL	2.0	24	-4.5 (1.50)	27	7.1 (1.41)	11.61 (2.06)	(8.16, 15.06)
	QTcF	2.0	24	-4.4 (1.39)	27	6.2 (1.31)	10.58 (1.91)	(7.37, 13.79)
	QTcB	2.0	24	-2.6 (1.92)	27	9.7 (1.81)	12.28 (2.64)	(7.85, 16.71)
Time 0	QTci	2.0	24	-2.2 (1.92)	27	11.8 (1.81)	13.95 (2.64)	(9.52, 18.39)
	QTciL	2.0	24	-2.2 (1.88)	27	11.9 (1.77)	14.09 (2.59)	(9.74, 18.43)
	QTcF	2.0	24	-2.1 (1.79)	27	11.3 (1.69)	13.38 (2.48)	(9.23, 17.54)
	QTcB	2.0	24	-4.2 (2.73)	27	11.0 (2.57)	15.27 (3.75)	(8.99, 21.55)

Delta: The difference between QTc at current time and QTc at baseline (average of time measures <0) for each patient
Delta 0: The difference between QTc at current time and QTc at Time 0 for each patient
LCL: Lower Confidence Limit UCL: Upper Confidence Limit

Source: Sponsor report (NN2211): Table 11.2, page 60 of 351

4.2.8.2.2 Categorical Analysis

The results from the categorical analyses by the sponsor were presented in Table 4. No subject's QTcI values >480 ms, and no change from baseline QTcI values >60 ms.

Table 4: Sponsor's Categorical Results

Dose*	Treatment	N	>=450 n (%) E	>=480 n (%) E	>=500 n (%) E	Increase >=30 n (%) E	Increase >=60 n (%) E
Baseline	Liraglutide	51	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0		
	Placebo	51	1 (2.0%) 1	0 (0.0%) 0	0 (0.0%) 0		
1.2	Liraglutide	50	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
	Placebo	50	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (2.0%) 1	0 (0.0%) 0
1.8	Liraglutide	51	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (2.0%) 1	0 (0.0%) 0
	Placebo	51	1 (2.0%) 1	0 (0.0%) 0	0 (0.0%) 0	2 (3.9%) 6	0 (0.0%) 0

Source: Sponsor report (NN2211): Table 14.2.17-1, page 184 of 351

4.2.8.2.3 Additional Analyses

In addition to QTcI, the sponsor also performed analyses based on other correction methods. The results are consistent with those using QTcI.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study.

Two withdrawals occurred due to the AEs of headache and pregnancy. This pregnancy resulted in a miscarriage at approximately 8 weeks of pregnancy. The miscarriage was deemed to have an "unlikely" casual relationship to study drug.

One subject in the placebo group experienced syncope.

In the crossover phase of the trial, more subjects reported an adverse event when treated with liraglutide, as compared to placebo (62.7% vs. 38.6%). Gastrointestinal disorders and decreased appetite accounted for the difference.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for liraglutide are presented in Table 5. PK exposure following 1.2 and 1.8 mg daily sc liraglutide administration produced exposure levels similar to the results seen in prior studies using these doses. The blood samples drawn for moxifloxacin were not analyzed for PK assessment.

Table 5: Liraglutide Pharmacokinetic Parameters – Per Protocol Population

Dose (mg/day)		N	Mean	SD	Median	Min	Max
1.2	C_{max} (pmol/L)	52	26387.1	11109.97	23374.5		
	t_{max} (hrs)	52	9.6	2.59	10.0		
	AUC (pmol/L*h)	52	459934.2	182526.54	418223.1		
1.8	C_{max} (pmol/L)	52	35806.3	11753.26	33227.5		
	t_{max} (hrs)	52	10.1	3.73	10.0		
	AUC (pmol/L*h)	52	648017.1	194718.79	663355.1		

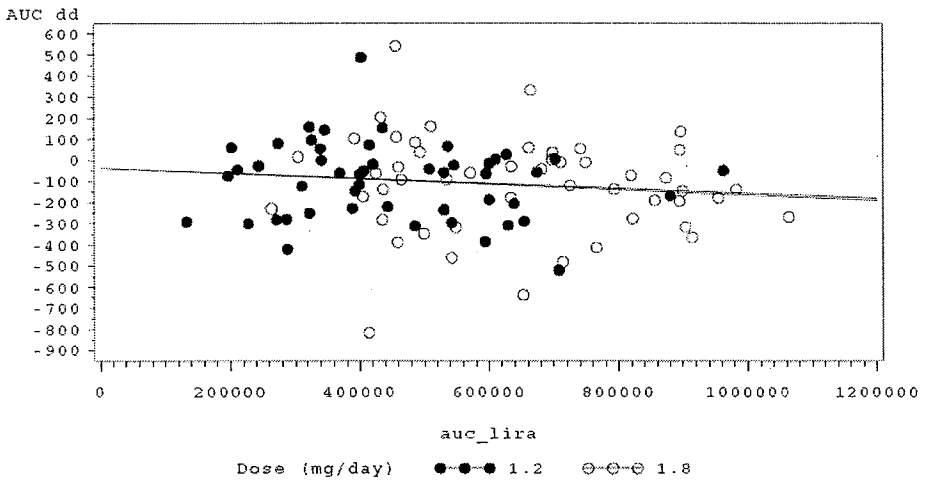
b(4)

Source: Table 11-10 (page 61) of sponsor's report NN2211-1644

4.2.8.4.2 Exposure-Response Analysis

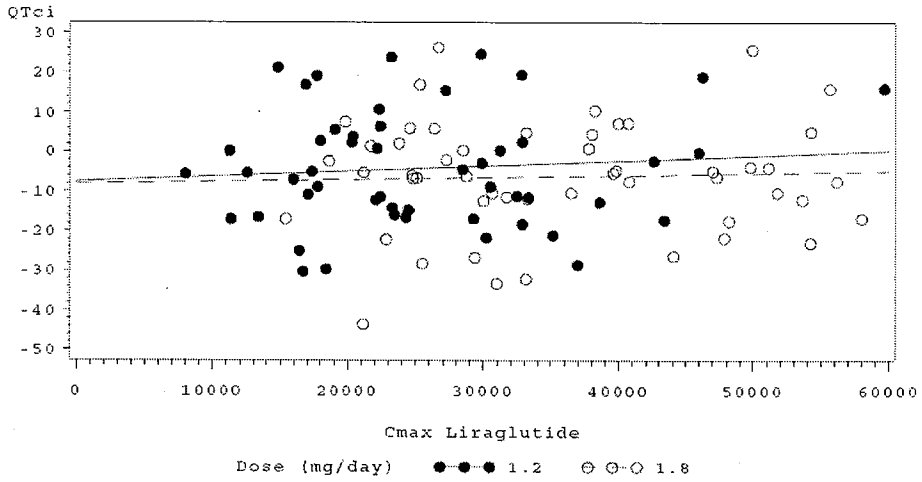
Exposure-response relationship was assessed as liraglutide AUC versus QTc effect. Plots of AUCQTc vs. drug AUC and ΔΔQTc vs. liraglutide Cmax do not show any particularly strong trend.

Figure 1: AUCQTc vs. drug AUC by Dose – Per Protocol Population



Source: Figure 11-1 (page 59) of sponsor's report NN2211-1644

Figure 2: ΔΔQTc vs. liraglutide Cmax – Per Protocol Population



Source: Figure 11-2 (page 59) of sponsor's report NN2211-1644

Reviewer's Comments: Sponsor's graphical exploratory analysis is inadequate because of the following reasons:

- *Area under Curve (AUC) is a summary statistic and it represents the exposure and effect for the entire duration of the sampling. Given the noise in QT measurements the maximum effect on QT interval is dampened.*
- *The exploration of the relationship between liraglutide C_{max} and ΔΔQTc at C_{max} is comparatively a reasonable approach. However, this approach fails to characterize the relationship in the event of a delay between the maximum plasma concentration and the effect on QT interval. Furthermore, there is a lot of imprecision in sampling the true T_{max}.*

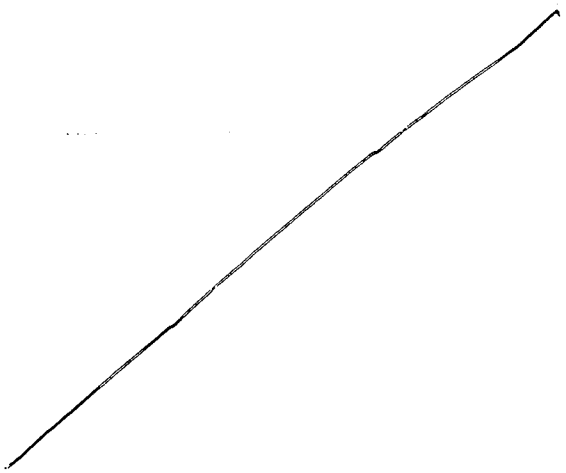
A plot of ΔΔQTc vs. drug concentrations is presented in Figure 8 *in Section 5.3 of Reviewer's Assessment.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The observed QT-RR interval relationship is presented in the following figure for different correction methods (QTcB, QTcF, QTcI) and RR.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



b(4)

We used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in the following Table 6, it appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment							
	All		Liraglutide		Moxifloxacian		Placebo	
method	n	MSSS	n	MSSS	n	MSSS	n	MSSS
QTcB	64	0.0032	59	0.0035	27	0.0057	81	0.0051
QTcF	64	0.0017	59	0.0020	27	0.0014	81	0.0018
QTcI	64	0.0004	59	0.0007	27	0.0010	81	0.0012

Note: +All: Combined all treatment groups
*MSSS: Mean of Sum of Squared Slope

5.2 STATISTICAL ASSESSMENTS

The statistical reviewer used the following data set to carry out the independent analyses for statistical evaluation of the results: qtpktm.xpt in QT-IRT eRoom.

5.2.1 QTcI Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The difference of baseline-adjusted QTcI between the treatment (liraglutide 1.8 mg and 1.2 mg) and the

placebo at each time point was analyzed using PROC MIXED procedure in SAS. The model includes TREMENT, PERIOD as fixed effects and SUBJECT as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following Table 7 and

Table 8, respectively.

The largest upper bounds of the 2-sided 90% CI for the mean difference between liraglutide 1.8 mg and placebo was 2.7 ms at 8 hours after dose. (See Table 7)

The largest upper bound of the 2-sided 90% CI for the mean difference between liraglutide 1.2 mg and placebo was 0.9 ms at 3 hours after dose. (See

Table 8)

Table 7: FDA Analysis Results of ΔΔQTcI for Liraglutide 1.8 mg

	Liraglutide 1.8 mg	Placebo	ΔΔQTcI	
Time/(hr)	ΔQTcI	ΔQTcI	Diff LS Mean	90% CI
3	-3.57	0.25	-3.83	(-7.2, -0.5)
6	-3.76	0.63	-4.39	(-7.1, -1.7)
8	-2.12	-2.41	0.29	(-2.1, 2.7)
9	-3.04	0.48	-3.52	(-6.6, -0.4)
10	-3.64	0.73	-4.37	(-7.5, -1.3)
10.5	-6.92	0.18	-7.10	(-9.8, -4.4)
11	-5.49	-0.28	-5.21	(-8.4, -2.0)
11.5	-7.28	-0.92	-6.36	(-8.9, -3.8)
12	-6.97	-0.19	-6.78	(-9.7, -3.9)
13	-5.67	-0.20	-5.47	(-8.6, -2.4)
16	-3.92	-1.25	-2.67	(-5.9, 0.6)
23.5	-4.08	1.17	-5.24	(-8.4, -2.1)

Table 8: FDA Analysis Results of ΔΔQTcI for Liraglutide 1.2 mg

	Liraglutide 1.2 mg	Placebo	ΔΔQTcI	
Time/(hr)	ΔQTcI	ΔQTcI	Diff LS Mean	90% CI
3	-0.43	1.27	-1.70	(-4.3, 0.9)
6	-2.76	1.11	-3.87	(-6.4, -1.3)
8	-2.86	-0.52	-2.33	(-5.2, 0.6)
9	-2.86	1.10	-3.95	(-6.9, -1.0)
10	-2.92	1.42	-4.34	(-6.9, -1.7)
10.5	-5.37	-1.64	-3.73	(-6.2, -1.3)
11	-5.84	0.12	-5.96	(-9.0, -2.9)
11.5	-5.51	0.90	-6.41	(-9.4, -3.4)
12	-4.94	-0.09	-4.86	(-8.5, -1.2)
13	-3.62	2.21	-5.83	(-8.7, -3.0)
16	-4.18	-1.52	-2.66	(-5.5, 0.2)
23.5	-3.38	1.55	-4.93	(-7.5, -2.3)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 8.9 ms (the corresponding mean is 12.4 ms) at 2 hours after dosing, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study. After Bonferroni adjustment (adjusted by 4 time points), the largest lower confidence interval is 7.6 ms.

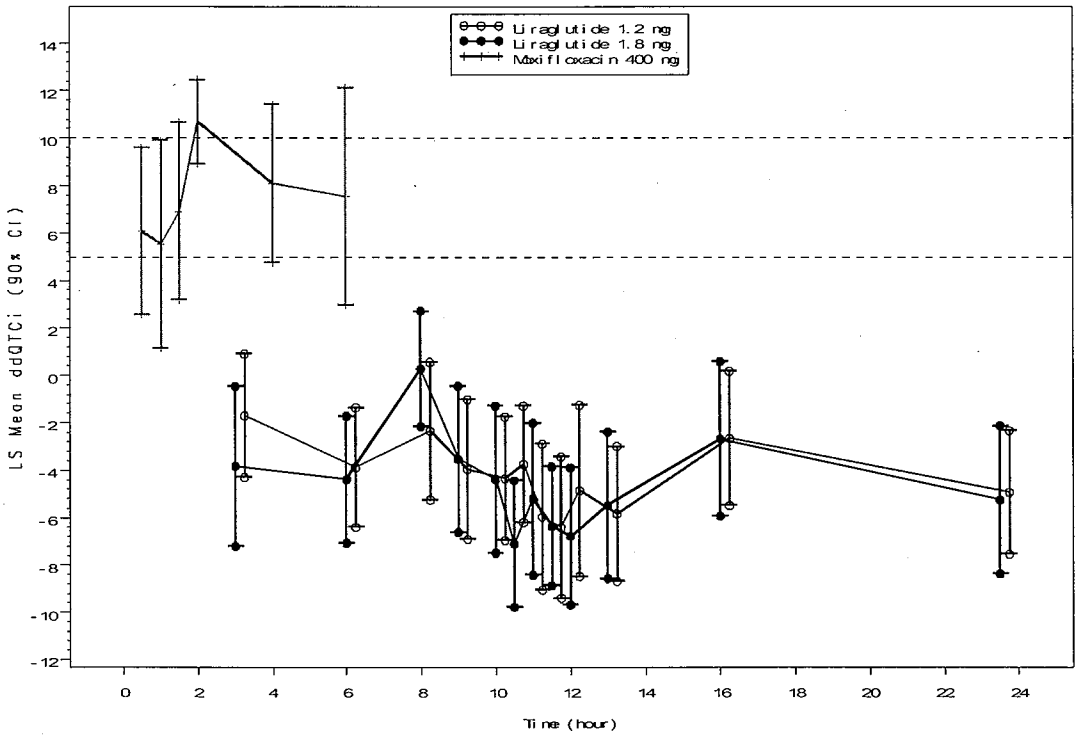
Table 9: FDA Analysis Results of ΔΔQTcI for Moxifloxacin

	Moxifloxacin	Placebo	ΔΔQTcI		
Time/(hr)	ΔQTcI	ΔQTcI	Diff LS Mean	90% CI	Adjusted* 90 % CI
0	-3.78	-1.71	-2.07	(-5.0, 0.9)	(-6.2, 2.0)
0.5	2.47	-3.60	6.07	(2.5, 9.6)	(1.2, 10.9)
1	5.29	-0.24	5.53	(1.1, 9.9)	(-0.5, 11.6)
1.5	6.02	-0.90	6.93	(3.2, 10.7)	(1.8, 12.1)
2	8.25	-4.19	12.43	(8.9, 15.9)	(7.6, 17.3)
4	-1.62	-9.72	8.10	(4.8, 11.4)	(3.5, 12.7)
6	-5.71	-13.3	7.54	(3.0, 12.1)	(1.2, 13.9)

*: Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

The following figure displays the time profile of ΔΔQTcI for different treatment groups.

Figure 4: Mean and 90% CI ΔΔQTcI Timecourse



5.2.1.3 Categorical Analysis

Categorical analyses of absolute QTcI and QTcI changes from baseline (ΔQTcI) are presented in Table 10 and Table 11, respectively. Both tables provide counts and percentages by the number of subjects as well as by the number of observations. There were no subjects whose absolute QTcI values were above 480 ms, nor were there any subjects whose ΔQTcI were above 60 ms.

Table 10: Categorical Analysis of QTcI - Liraglutide 1.8 mg/day

	Total N		Value<=450		450<Value<=480	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Liraglutide	59	2119	59 (100%)	2119 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	27	297	25 (92.6%)	289 (97.3%)	2 (7.4%)	8 (2.7%)
Placebo	57	2093	55 (96.5%)	2091 (99.9%)	2 (3.5%)	2 (0.1%)
PlaceboMx	24	264	23 (95.8%)	260 (98.5%)	1 (4.2%)	4 (1.5%)

Table 11: Categorical Analysis of ΔQTcI

	Total N		Value<=30		30<Value<=60	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Liraglutide	59	2119	58 (98.3%)	2118 (100%)	1 (1.7%)	1 (0.0%)
Moxifloxacin	27	297	27 (100%)	297 (100%)	0 (0.0%)	0 (0.0%)
Placebo	57	2093	54 (94.7%)	2086 (99.7%)	3 (5.3%)	7 (0.3%)
PlaceboMx	24	264	24 (100%)	264 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis was performed based on baseline adjusted PR intervals. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the PR mean differences between liraglutide 1.8 mg and placebo is 12.4 ms at 3 hours after dosing. Figure 5 displays the time profile of ΔΔPR.

The outlier analysis results for PR are presented in Table 13. There are 3 subjects who experienced absolute PR interval greater than 200 ms in liraglutide 1.8-mg group.

Figure 5: Mean and 90% CI ΔΔPR Timecourse

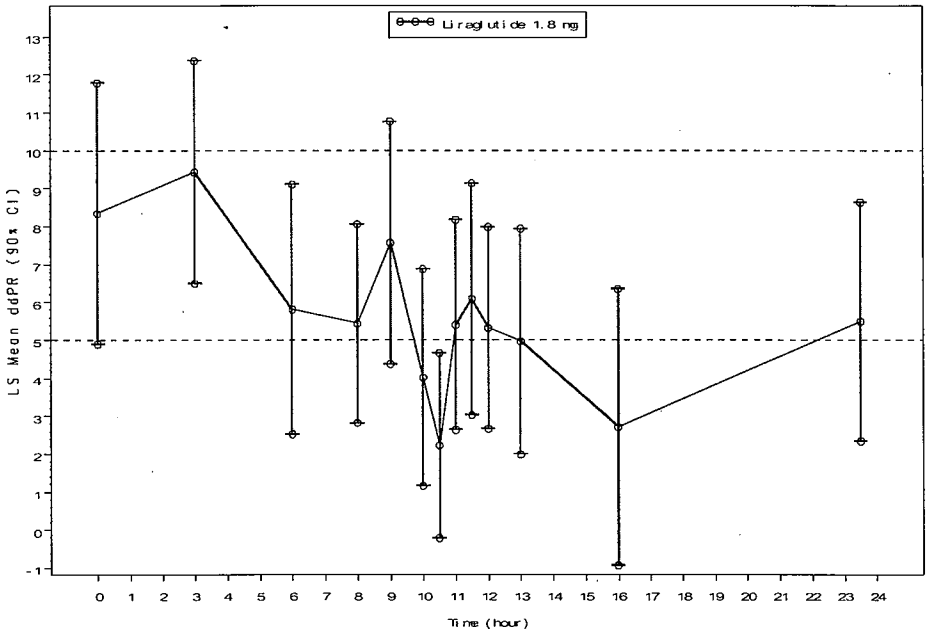


Table 12: FDA Analysis Results of ΔΔPR for Liraglutide 1.8 mg/day

	Liraglutide 1.8 mg	Placebo	ΔΔPR	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	5.58	-2.77	8.34	(4.9, 11.8)
3	7.24	-2.19	9.43	(6.5, 12.4)
6	5.59	-0.22	5.81	(2.5, 9.1)
8	4.82	-0.61	5.43	(2.8, 8.1)
9	6.88	-0.68	7.57	(4.4, 10.8)
10	3.33	-0.69	4.01	(1.2, 6.9)
10.5	2.58	0.36	2.22	(-0.2, 4.7)
11	4.83	-0.57	5.40	(2.6, 8.2)
11.5	4.63	-1.45	6.08	(3.0, 9.1)
12	3.84	-1.48	5.32	(2.7, 8.0)
13	3.75	-1.21	4.96	(2.0, 7.9)
16	2.20	-0.51	2.71	(-0.9, 6.3)
23.5	2.15	-3.34	5.49	(2.3, 8.6)

Table 13: Categorical Analysis of PR

	Total N		Value<200		Value>=200	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	59	767	54 (91.5%)	734 (95.7%)	5 (8.5%)	33 (4.3%)
Liraglutide 1.8mg	52	676	49 (94.2%)	657 (97.2%)	3 (5.8%)	19 (2.8%)

5.2.3 QRS Analysis

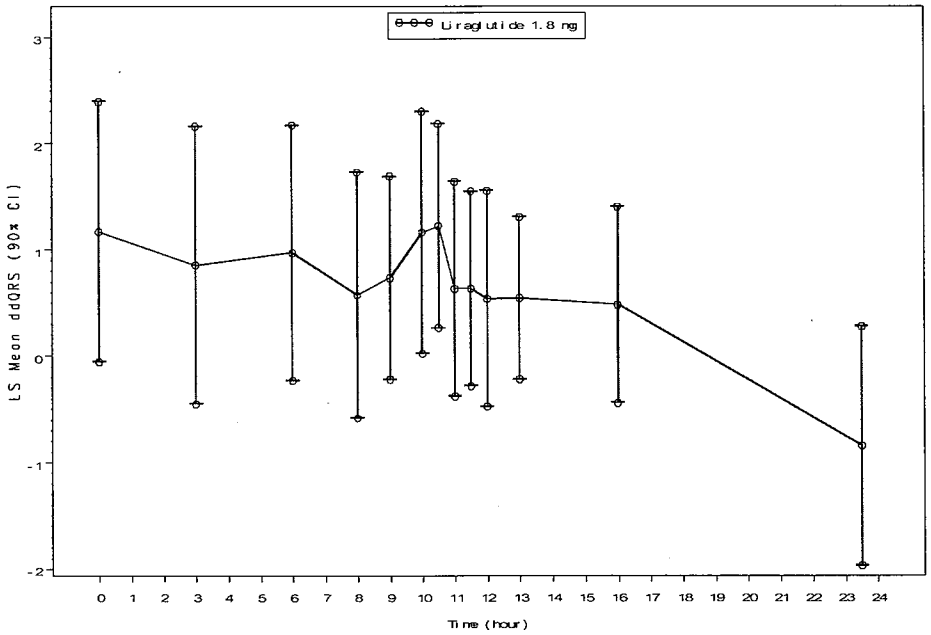
The same statistical analysis was performed based on baseline adjusted QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limit of 90% CI for the QRS mean differences between liraglutide 1.8 mg and placebo is 2.2 ms after 10.5 hours post-dosing

Table 14: FDA Analysis Results of ΔΔQRS for Liraglutide 1.8 mg/day

	Liraglutide 1.8 mg	Placebo	ΔΔQRS	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	-0.30	-1.47	1.17	(-0.1, 2.4)
3	0.31	-0.54	0.86	(-0.4, 2.2)
6	0.84	-0.13	0.97	(-0.2, 2.2)
8	0.59	0.01	0.58	(-0.6, 1.7)
9	0.06	-0.68	0.74	(-0.2, 1.7)
10	1.56	0.40	1.16	(0.0, 2.3)
10.5	0.70	-0.53	1.23	(0.3, 2.2)
11	0.73	0.10	0.63	(-0.4, 1.6)
11.5	0.51	-0.13	0.63	(-0.3, 1.5)
12	0.27	-0.27	0.54	(-0.5, 1.6)
13	0.15	-0.40	0.55	(-0.2, 1.3)
16	-0.11	-0.60	0.48	(-0.4, 1.4)
23.5	-0.71	0.13	-0.84	(-2.0, 0.3)

The following figure displays the time profile of ΔΔQRS.

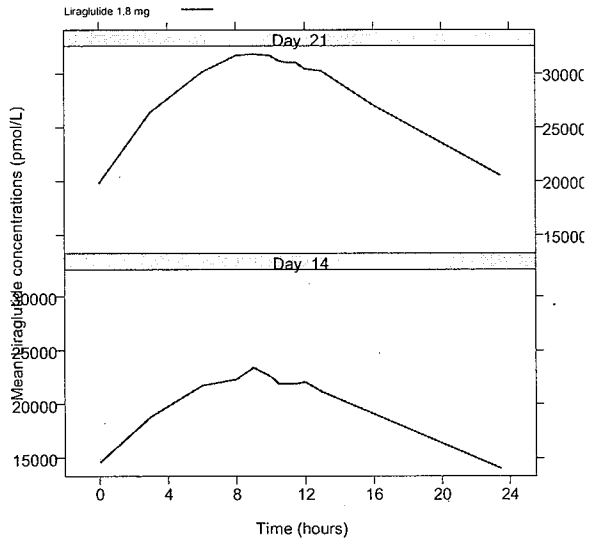
Figure 6: Mean and 90% CI ΔΔQRS Timecourse



5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

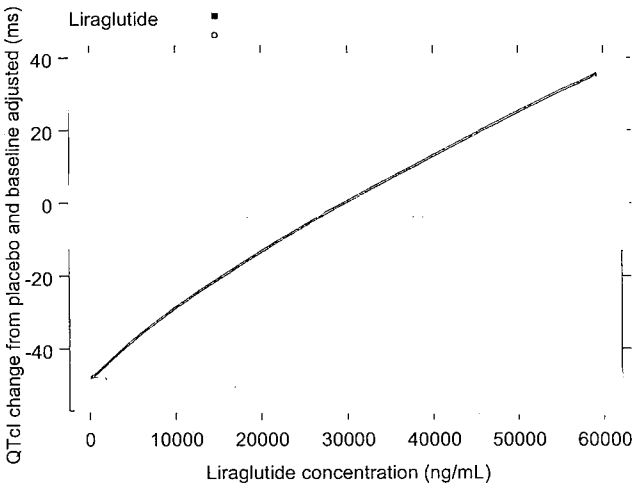
The mean drug concentration-time profile is illustrated in Figure 7.

Figure 7: Mean Liraglutide Concentration-time Profiles for Liraglutide (Day 21 Represents 1.8 mg and Day 14 Represents 1.2 mg doses Respectively)



The relationship between ΔΔQTcI and liraglutide concentrations is visualized in Figure 8 with no evident exposure-response relationship.

Figure 8: ΔΔ QTcI vs. Liraglutide Concentration



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5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study with liraglutide.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 93% of the ECGs were annotated in the primary lead II, with less than 0.1% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS intervals

Liraglutide (1.8 mg) increased the PR interval with a maximum baseline and placebo corrected difference of 9.43 ms at 3 hours (upper bound of 90% CI-12.4 ms). However this finding is not clinically relevant, since the three subjects who had an absolute PR greater than 200 ms post-treatment also had an elevated PR at baseline. For the QRS interval, the largest upper bound of the 90% CI for baseline and placebo adjusted change was 2.2 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<table>
<tr><td>Therapeutic dose</td><td colspan="2">For all patients liraglutide should be initiated with once daily doses of 0.6 mg for at least one week, after which the dose should be increased to daily doses of 1.2 mg. Based on clinical response and after at least one week the dose can be increased to 1.8 mg to achieve maximum efficacy.</td></tr>
<tr><td>Maximum tolerated dose</td><td colspan="2">For single dose administration to healthy young male subjects; the maximum tolerable dose was 17.5 µg/kg (~ mean 1.33 mg, range 1.16-1.49 mg). Higher doses are tolerated, when administered in a stepwise dose increase regimen.</td></tr>
<tr><td>Principal adverse events</td><td colspan="2">The most frequent adverse events are from the gastro intestinal organ class (nausea, diarrhea and other GI symptoms). The weekly dose increase from 0.6 mg/day to 1.2 mg/day and 1.8 mg/day is introduced to mitigate gastrointestinal symptoms.</td></tr>
<tr><td rowspan="3">Maximum dose tested</td><td>Single Dose</td><td>The maximum single dose administered in clinical pharmacology trials is 20 µg/kg (~ mean 1.44 mg (range: 1.26–1.71 mg)).</td></tr>
<tr><td>Multiple Dose</td><td>The maximum multiple daily doses administered in clinical pharmacology trials is 1.8 mg.

The maximum dose of 1.8 mg is reached by daily administrations of liraglutide 0.6 mg for one week, liraglutide 1.2 mg for one week followed by liraglutide 1.8 mg for 1-2 weeks.

(Stepwise dose escalation to liraglutide 2 mg has been administered in an early phase 2 trial, but pharmacokinetic data is not available to provide total exposure and maximum concentration).</td></tr>
<tr><td></td></tr>
<tr><td rowspan="2">Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>Single dose administration of 20 µg/kg (~ mean of 1.44 mg, range: 1.26–1.71 mg):
<table><tr><td></td><td>Mean (SD)</td><td>CV %</td></tr><tr><td>AUC pmol/h/L</td><td>523224 (104999)</td><td>19</td></tr><tr><td>Cmax pmol/L</td><td>20209 (2981)</td><td>15</td></tr></table></td></tr>
<tr><td>Multiple Dose</td><td>Multiple dose administrations of liraglutide 1.8 mg, steady state exposures:
<table><tr><td></td><td>Mean (SD)</td><td>CV %</td></tr><tr><td>AUC$_\tau$ pmol/h/L</td><td>809121 (186605)</td><td>23</td></tr><tr><td>Cmax pmol/L</td><td>44663 (10524)</td><td>24</td></tr></table></td></tr>
</table>

Range of linear PK	Dose proportionality was shown for AUC and C_{max} following single dose administration in the dose range 2.5 µg/kg (~ mean 0.18 mg) to 20 µg/kg (~ mean 1.44 mg). Further, dose proportionality for AUCτ for liraglutide doses of 1.2 and 1.8 mg could be assumed. An exploratory analysis of sparse sampling concentration data from an early phase 2 trial demonstrated dose proportionality across the entire dose range 0.5 – 2 mg.	
Accumulation at steady state	The mean accumulation ratio estimated on steady state liraglutide 10 µg/kg was 1.45 (SD 0.14); CV%=10. Across the dose range of 5-12.5 µg/kg, the accumulation ratio was 1.4-1.5. Based on liraglutide concentrations following a single dose of 0.6mg followed by stepwise dose increase to steady state 1.8 mg, the mean dose adjusted accumulation ratio was estimated to 1.8.	
Metabolites	Following administration of a single dose of tritium labelled liraglutide, the metabolite profiles in plasma, urine and faeces were investigated. Intact liraglutide was the major component detected in plasma; two metabolites were identified, below 5 and 9 % of total exposure in plasma. No intact liraglutide was detected in either urine or faces and only minor metabolites were present in urine and faeces (< 3% and 3-5% in urine and faeces of total radioactivity, respectively). No unique human metabolite was identified.	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability (dose 5 µg/kg): 55 % (SD 37%).
	Tmax	• Median (range) for parent Following a single dose of 20 µg/kg (~ mean 1.44 mg), tmax (median (min-max)) was: 10 h (8-12) • Median (range) for metabolites: NA, since no major metabolites have been identified
Distribution	Vd/F or Vd	Across the liraglutide doses administered, the volume of distribution ranged 11-17L. Following a single s.c. dose of 20 µg/kg (~ mean 1.44 mg), mean V_z/F was 0.14 L/kg (SD 0.02); CV%=14.
	% bound	Plasma protein binding was > 98%.
Elimination	Route	Liraglutide is metabolised similarly to native GLP-1 (i.e. by DPP-IV and NEP) but at a much slower rate. The combined in vitro and in vivo animal and human data suggest that liraglutide is fully degraded in the body with no single organ as major route of elimination.

<table>
<tr><td></td><td></td><td>• Other routes: NA</td></tr>
<tr><td></td><td>Terminal t½</td><td>Across trials, T ½ was approximately 13 h (range 9-15 h).

Following a single s.c. dose of 20 µg/kg (~ mean 1.44 mg), mean t ½ was 11 h (SD 2h); CV%=18.

• Mean (%CV) for metabolites: NA; as no major metabolites have been identified</td></tr>
<tr><td></td><td>CL/F or CL</td><td>CL/F: 0.0131 L/h/kg (CV% 31.8) (population pharmacokinetic analysis)</td></tr>
<tr><td>Intrinsic Factors</td><td>Age</td><td>Comparison of AUC_{0-t} and C_{max} for Liraglutide between elderly and young healthy subjects. No effect of age was demonstrated.
<table>
<tr><td></td><td>AUC_{0-t}
Ratio [90% CI]</td><td>C_{max}
Ratio [90% CI]</td></tr>
<tr><td>Elderly/young</td><td>0.94 [0.84; 1.06]</td><td>0.94 [0.84; 1.05]</td></tr>
</table></td></tr>
<tr><td></td><td>Sex</td><td>Comparison of AUC_{0-t} and C_{max} for Liraglutide between female and male healthy subjects.
<table>
<tr><td></td><td>AUC_{0-t}
Ratio [90% CI]</td><td>C_{max}
Ratio [90% CI]</td></tr>
<tr><td>Female/male</td><td>1.08 [0.93; 1.26]</td><td>0.96 [0.83; 1.11]</td></tr>
</table>
In contrast to the results in healthy subjects following single dose administration; a population pharmacokinetic analysis showed lower CL/F (weight adjusted) for female subjects (0.0115 L/h/kg) than for male subjects (0.0151 L/h/kg). Inter-subject variation was 29% (CV%).</td></tr>
<tr><td></td><td>Race</td><td>A population pharmacokinetic analysis investigated the effect of race on weight adjusted CL/F (i.e. exposure). In the full covariate model which also included gender effect on CL/F, the effect of race was not significant at the pre-specified significance level of 0.1% on backward elimination of the covariate.</td></tr>
<tr><td></td><td>Hepatic & Renal Impairment</td><td>Exposure was not elevated in subjects with renal or hepatic impairment compared to subjects with normal renal or hepatic function.
Comparison of $AUC_{0-\infty}$ and C_{max} for Liraglutide between Renal Groups</td></tr>
</table>

	$AUC_{0-\infty}$ Ratio [90% CI]	C_{max} Ratio [90% CI]
Mild/normal	0.67 [0.54; 0.85]	0.75 [0.57, 0.98]
Moderate/normal	0.86 [0.70; 1.07]	0.96 [0.74, 1.23]
Severe/normal	0.73 [0.57; 0.94]	0.77 [0.57; 1.03]
ESRD/normal	0.74 [0.56; 0.97]	0.92 [0.67; 1.27]

N: Normal=6; Mild=6; Moderate=7; Severe=5; ESRD=6

The statistical analysis was adjusted for effect of age and body weight

of $AUC_{0-\infty}$ and C_{max} for Liraglutide between Hepatic Groups

	$AUC_{0-\infty}$ Ratio [90% CI]	C_{max} Ratio [90% CI]
Mild/normal	0.77 [0.53; 1.11]	0.89 [0.65; 1.21]
Moderate/normal	0.87 [0.60; 1.25]	0.80 [0.59; 1.09]
Severe/normal	0.56 [0.39; 0.81]	0.71 [0.52; 0.97]

N: Normal=6; Mild=6; Moderate=6; Severe=6

The statistical analysis was adjusted for effects of age, gender and body weight.

Extrinsic Factors	Drug interactions	

Comparison of $AUC_{0-\infty}$ and C_{max} between Liraglutide (1.8 mg) and placebo for paracetamol, atorvastatin, griseofulvin, lisinopril, digoxin and ethinylestradiol / levonorgestrel

Oral Drug	Dose	N[a]	$AUC_{0-\infty}$ Ratio [90% CI]	C_{max} Ratio [90% CI]
paracetamol	1.0 g	18	1.04 [0.97; 1.10]	0.69 [0.56; 0.85]
Atorvastatin	40 mg	42	0.95 [0.89; 1.01]	0.62 [0.53; 0.72]
Griseofulvin	500 mg	22	1.10 [1.01; 1.19]	1.37 [1.24; 1.51]
Lisinopril	20 mg	40	0.85 [0.75; 0.97]	0.73 [0.63; 0.85]
Digoxin	1 mg	27	0.84 [0.72; 0.98][b]	0.69 [0.60; 0.79]
Ethinylestradiol[c]	0.03 mg	21	1.06 [0.99:1.13]	0.88 [0.79;0.97]
Levonorgestrel[c]	0.15 mg	14	1.18 [1.04;1.34][b]	0.87 [0.75;1.00]

[a] Number of subjects included in analysis of AUC

[b] Digoxin: AUC_{0-72h}, levonorgestrel: equivalence was demonstrated for AUC_{0-t} with similar ratio

		[c] Ethinylestradiol and levonorgestrel given in a combination oral contraceptive product
	Food Effects	NA
Expected High Clinical Exposure Scenario		A 65-year old male accidental took an overdose of liraglutide. On ——. ←—— the subject was admitted to the hospital at 10:40 hrs due to an accidental overdose of liraglutide and symptoms of gastritis. Reportedly, the subject had administered the first dose of trial drug on 10-Sep-2006 around 10:30 hrs. Starting ——— , at 12:30 hrs the subject experienced 10-15 episodes of sweating, vomiting and abdominal discomfort. A drug count revealed that the subject accidentally administered 17.4 mg of liraglutide instead of the prescribed 10 click (0.6 mg). Examination at admission to the hospital gave the following vital sign results: blood pressure of 130/80 mm Hg, pulse rate of 90 beats/min, respiratory rate of 18/min and a blood glucose value of 114 mg/dL. ECG was found to be normal. Memory disturbances with regards to names and calculations were noted. Blood sugars, electrolytes, liver and renal functions were monitored regularly while the subject was admitted. To relieve the subject, treatment with Ondansetron, ranitidine, dextrose 10% and normal saline was commenced. The subject was discharged and considered fully recovered on ——— Liraglutide concentrations were not measured. Subject was withdrawn from the trial.

b(6)

6.2 TABLE OF STUDY ASSESSMENTS

2 Flow Chart (Trial Related Procedures)

	Screen	← Treatment (liraglutide or placebo) →					Moxifloxacin or placebo		Phone Follow-up
Visit →	Visit 1	Visit 2 & 7	Visit 3 & 8[D]	Visit 4 & 9	Visit 5 & 10[D]	Visit 6 & 11	Visit 12		Visit 13
Study Day →	-14	-1 to 1 & 27 – 29 (± 3)	2 – 13 & 30 – 41 (±3)	14 & 42 (±3)	15 – 20 & 43 – 48 (± 3)	21 & 49 (± 3)	56 (± 3)	57 (± 3)	67 ± 3
Procedure↓									
1. Informed Consent/HIPPA	X								
2. Demographic info.	X								
3. Medical history/ concomitant illness	X								
4. Concomitant medication	X	X	X	X	X	X	X		X
5. Inclusion/Exclusion criteria	X								
6. Withdrawal criteria		X		X		X	X		
7. Randomization		X							
8. Complete physical exam,	X							X	
9. Targeted physical exam				X		X	X		
10. Weight	X							X	
11. Height	X								
12. Vital Signs	X			X		X		X	
13. Hematology/differential/biochemistry[E]	X							X	
14. Urinalysis	X							X	
15. Hepatitis B and C, HIV	X								
16. Urine Drug/alcohol Screen/Cotinine	X								
17. Telephone Contact									X
18. Conventional/Serial ECG	X	X[A]		X[A]		X[A]		X[A]	
20. Liraglutide/placebo/moxi dosing[B]			X	X	X	X		X	
21. PK Blood draws[C] liraglutide/moxifloxacin[D]				X		X		X	
22. Adverse Events		X	X	X	X	X	X	X	X
23. Drug accountability								X	
24. End of Trial Form									X

A. Serial ECG monitoring (as in Section 8.2.1) on days 0, 28 and 56 (for baseline QTc). On Days 14 (& 42) and 21 (& 49) serial ECG will be collected for 24 hours (6 hrs on Day 57 post moxifloxacin dosing)

B. Liraglutide daily dose (sc) - 0.6 mg on Days 1-7 (& 29-35), 1.2 mg/day on Days 8-14 (& 36-42) and 1.8 mg/day on Days 15-21 (& 43-49). Single dose 400 mg moxifloxacin administered on Day 57.

C. Serial (24-hr) serum PK samples will be collected on Days 8 (& 35) and 12 (& 37) for liraglutide (optional PK samples will be collected for only 6 hours post moxifloxacin/no-treatment on Day 57 – only for patients on moxifloxacin)

D. Subjects will have their daily dose administered at home by a Study nurse or in the clinic every morning at 7:00 AM (± 2 hours)

E. At baseline only serum β-hCG pregnancy test (in females)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joanne Zhang
1/5/2009 12:07:17 PM
BIOMETRICS
Dr. Park Misook was the primary statistical reviewer for this NDA.

Christine Garnett
1/5/2009 12:17:13 PM
BIOPHARMACEUTICS

Rajnikanth Madabushi
1/6/2009 09:47:23 AM
BIOPHARMACEUTICS

Suchitra Balakrishnan
1/6/2009 10:12:40 AM
MEDICAL OFFICER

Norman Stockbridge
1/6/2009 04:09:55 PM
MEDICAL OFFICER